SPECIAL ISSUE: DIABETES, CARDIOVASCULAR AND RENAL OUTCOMES

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ALSO IN THIS ISSUE

CONNECTING DIABETES AND RENAL OUTCOMES. Starting with the annoucement of results from CREDENCE in April, the news at major scientific meetings has focused on the connections between diabetes and the cardiovascular and renal systems, and the potential for newer drug classes to protect kidney function, SP233-SP236.

TIME-IN-RANGE GUIDELINES. Work by an international committee led to the first guidelines from the American Diabetes Association (ADA) on how many hours per day users of continuous glucose monitoring (CGM) systems should be in range, SP238.

REAL-WORLD EVIDENCE. Abbott reports at ADA that those with type 2 diabetes using its FreeStyle Libre Flash CGM lowered their glycated hemoglobin by 0.9%, with no differences among subgroups, SP239.

SHOULD CARDIOLOGISTS PRESCRIBE SGLT2S? In Los Angeles, the Institute for Value-Based Medicine® reviewed evidence from cardiovascular outcomes trials for sodium glucose cotransporter 2 (SGLT2) inhibitors and other type 2 diabetes therapies, as well as the future of CGM and the role of cardiologists in diabetes care, SP240.

BUTLER WATSON PETERS JAIN

PHARMACY PERSPECTIVE

Outcomes Trials Set Stage for Future of Diabetes Management in Patients With Renal Disease

Joseph E. Cruz, PharmD, BCPS; and Mary Barna Bridgeman, PharmD, BCPS, BCGP

THE EVIDENCE FOR OPTIMAL management of diabetes continues to evolve at a feverish pace. Since the FDA introduced its guidance on evaluating the cardiovascular risk of new diabetes drugs in 2008, investigators have made significant progress in amassing evidence that therapeutic agents reduce the risk of major clinical end points.[1] These clinical advances are best represented by data from pivotal trials demonstrating a reduction in major adverse cardiovascular events (MACE) associated with both the sodium glucose cotransporter type 2 (SGLT2) inhibitors and the glucagon-like peptide-1 (GLP-1) receptor agonists in particular. The dipeptidyl peptidase 4 (DPP-4) inhibitors have not been shown in major investigations to increase cardiovascular risk. Large, prospective, cardiovascular outcomes studies have demonstrated the efficacy of various agents from the SGLT2 inhibitor and GLP-1RA classes in reducing MACE, including EMPA-REG OUTCOME (empagliflozin),[2] CANVAS (canagliflozin),[3] LEADER (liraglutide),[4] and SUSTAIN 6 (semaglutide).[5] In fact, the American Diabetes Association (ADA)'s *Standards of Medical Care in Diabetes—2019* has incorporated the evidence from these studies to guide clinicians on which therapies may be optimal in patients with established atherosclerotic

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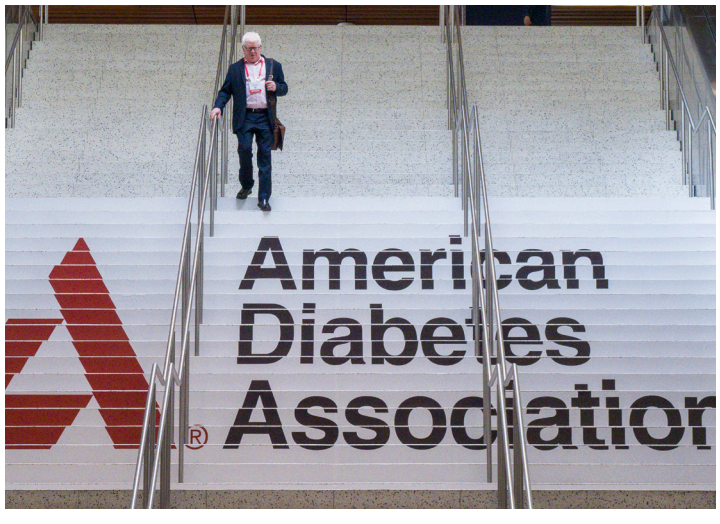

Robert A. Gabbay, MD, PhD, FACP, chief medical officer and senior vice president at Joslin Diabetes Center, arrives at the 79th American Diabetes Association Scientific Sessions. Gabbay is editor-in-chief of *Evidence-Based Diabetes Management*™; see **SP224**.

INDUSTRY PERSPECTIVE

AstraZeneca's Khan Discusses Dapagliflozin and Cardiovascular, Renal Outcomes in Diabetes Care

Mary Caffrey

OVER THE PAST DECADE, results from cardiovascular outcomes trials (CVOTs) for glucose-lowering therapies have had an enormous impact on people with type 2 diabetes (T2D). The first wave of findings reported on major adverse cardiovascular events (MACE) that were the focus of the FDA's 2008 guidance requiring the studies.[1] In November 2018, the DECLARE-TIMI trial reported results for dapagliflozin, the sodium glucose cotransporter 2 (SGLT2) inhibitor sold as Farxiga by AstraZeneca.[2] Those results showed that dapagliflozin significantly reduced the risk of hospitalization for heart failure and appeared to slow the loss of kidney function.

That second finding reflects a major focus in a new wave of findings for SGLT2 inhibitors. The first

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CLINICAL TRIAL

CREDENCE: First Renal Outcomes Trial Finds Canagliflozin Cuts Risk of Renal Failure, Death; Prompts ADA Updates

Mary Caffrey

CREDENCE, the first of a coming wave of dedicated renal outcomes trials for sodium glucose cotransporter 2 (SGLT2) inhibitors, has reported 2 sets of results that suggest there is more news to come for the drug class that has already changed diabetes care since reaching the market in 2013.[1]

Investigators for CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation), reported on April 14, 2019, that

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FROM THE CHAIRMAN

Learning What Else Today's Type 2 Diabetes Drugs Can Do

MORE THAN A DECADE AGO, the FDA faced concerns that rosiglitazone (Avandia), then a top-selling drug to treat type 2 diabetes (T2D), might increase the risk of heart attacks. Although the meta-analysis that raised the alarm became the subject of debate,[1] its lead author, Steven E. Nissen, MD, of Cleveland Clinic, raised an important point: Regulators did not require makers of glucose-lowering therapies to study whether the drugs caused heart attacks, strokes, or cardiovascular death.

With support from cardiologist Robert M. Califf, MD, who would go on to lead the FDA, Nissen convinced the agency to adopt a guidance that created the cardiovascular outcomes trials (CVOTs). These studies have shaped diabetes care more than their advocates might have imagined. As Nissen told *Evidence-Based Diabetes Management*™ last fall, not only have CVOTs uncovered some unanticipated problems with a few therapies,[2] but, "We also knew that if you did outcomes trials, you would learn things you didn't otherwise know."

CVOTs have been especially useful for revealing the multiple uses of sodium glucose cotransporter 2 (SGLT2) inhibitors, which have a unique mechanism that targets a protein that normally reabsorbs glucose in the renal system. At first, the focus was on the big surprises: the reduction in cardiovascular death seen in EMPA-REG OUTCOME,[3] the reduction in major adverse cardiovascular events seen in CANVAS,[4] and the reduction in a primary end point of cardiovascular death and heart failure seen in DECLARE-TIMI.[5]

Now, attention is turning to the microvascular results seen in those trials, as well as the resulting new studies namely the dedicated trials that are examining SGLT2 inhibitors in heart failure and their ability protect the kidney from the decline normally seen in people who live a long time with T2D. This spring, separate analyses of renal data from CVOTs and results from the first dedicated renal outcomes trial, CREDENCE,[6] showed the value of this class for managed care: Not only do they treat T2D, but they have the potential to keep patients from progressing to dialysis—one of the most expensive, debilitating, and invasive situations in all of healthcare. The cost-effectiveness analyses are not all in, but they are under way, and we look forward to these results. ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

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FROM THE EDITOR-IN-CHIEF

Evolving Role of T2D Therapy: From Secondary to Primary Prevention


GABBAY

CARDIOVASCULAR DISEASE (CVD) IS the leading cause of death in the world, and the top killer of those with diabetes. Having diabetes doubles the risk of death from CVD, and women are at particularly high risk. Despite this, for years a diabetes drug was measured by only its ability to lower blood glucose. Cholesterol-lowering statins or angiotensin converting enzyme inhibitors that controlled blood pressure did the heavy lifting in management of cardiovascular (CV) risk. But over the past decade, we have seen a paradigm shift, not only in what we can expect from a diabetes therapy, but also in our knowledge that drugs developed for diabetes could be used to treat other complications, or even *prevent* them from happening in the first place.

The shift began in 2008, when FDA declared that the old definition of success—lowering glycated hemoglobin (A1C)—was not enough for the next wave of diabetes drugs. Under a new guidance, the test would include outcomes: is a drug safe? Can we be certain that a person taking the drug is not more likely to have a heart attack or stroke?

We welcomed the unexpected news: drugs in 2 classes—the sodium glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists—could, in some cases, reduce CV events and even death. But there was also evidence that the SGLT2 inhibitors, in particular, could reduce the risk of hospitalization for heart failure and renal decline.

As it became clear these diabetes drugs might slow the loss of losing kidney function, a new wave of outcomes trials began—this time to examine the drugs' potential in primary prevention. A drug developed for one purpose—to control blood glucose and lower A1C—might be used to keep patients from developing diabetic kidney disease, which affects about 1 in 4 people with diabetes, or from progressing to dialysis, one of the most expensive and debilitating conditions in all of healthcare. The first of the renal outcomes trials, CREDENCE, reported in April that the SGLT2 inhibitor canagliflozin reduced the risk of renal failure and death by 30% in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD).[1] At the American Diabetes Association (ADA) Scientific Sessions this month, held in San Francisco, California, results from the REWIND trial showed that the GLP-1 receptor agonist dulaglutide reduced CV events 12% and showed renal benefits in a cohort that for the first time included a large primary prevention population.[2] When viewed with other trial results and real-world data, these findings open doors for collaboration among endocrinologists, cardiologists and nephrologists, to vastly improve the prospects for those at risk of diabetic kidney disease. This will deepen the ties between ADA and the American College of Cardiology (ACC), which have jointly endorsed guidelines on the use of SGLT2 inhibitors and GLP-1 receptor agonists for patients who have CV risk and T2D.

The challenge now is getting payers to embrace the evidence. Because of increased obesity, the numbers with CKD had been projected to rise, but these new results suggest the trend can be slowed or even reversed, if the right patients receive the right drugs. Unfortunately, new diabetes drugs are reaching only a fraction of patients who could benefit. Survey results reported at the 2018 ADA Scientific Sessions showed 28% of physicians said their patients were unable to start new diabetes therapy, and SGLT2 inhibitors in particular, due to cost.

Collaboration between ADA and ACC, and the recent joint session between ADA and the American Society of Nephrology in San Francisco show that specialists are ready work together in the cause of prevention. It's time for reimbursement to keep pace with the science, both to help patients and to prevent unnecessary spending years from now. ◆

Robert A. Gabbay, MD, PhD, FACP
EDITOR-IN-CHIEF

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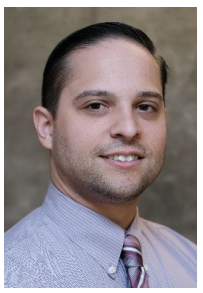
PHARMACY PERSPECTIVE

Outcomes Trials Set Stage for Future of Diabetes Management in Patients With Renal Disease

Joseph E. Cruz, PharmD, BCPS, and Mary Barna Bridgeman, PharmD, BCPS, BCGP



CRUZ

Joseph E. Cruz, PharmD, BCPS

BRIDGEMAN

Mary Barna Bridgeman, PharmD, BCPS, BCGP

continued from cover

cardiovascular disease or other comorbidities, such as chronic kidney disease (CKD).[6]

Numerous opportunities remain to advance the science regarding optimization of diabetes treatment in reducing the risk of microvascular and macrovascular manifestations of diabetes. Further, investigators have presented several studies at the ADA's 79th Scientific Sessions, June 7-11, 2019, in San Francisco, California (see **SP233-SP236**). Some of the Scientific Sessions presentations demonstrating results from these anticipated outcomes studies are highlighted below.

Investigators have conducted a number of trials to evaluate the effects of the SGLT2 inhibitors in slowing the progression of CKD as well as the progression of kidney disease as a secondary outcome. In a post hoc analysis of the EMPA-REG OUTCOME trial, renal outcomes associated with empagliflozin—including incident or worsening nephropathy or progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy, and death from renal disease—were evaluated.[7] A total of 7020 patients received at least 1 dose of study medication, with the following outcomes:

- Incident or worsening nephropathy occurred in 525 of the 4124 patients (12.7%) receiving empagliflozin and in 388 of 2061 patients (18.8%) receiving placebo (hazard ratio [HR] for empagliflozin, 0.61; 95% CI, 0.53-0.70; P <.001).
- Progression to macroalbuminuria occurred in 459 of 4091 patients (11.2%) receiving empagliflozin compared with 330 of 2033 (16.2%) in the placebo group, representing a 38% reduction in risk of progression of kidney disease (HR for empagliflozin, 0.62; 95% CI, 0.54-0.72; P <.001).
- A doubling of serum creatinine occurred in 70 of the 4645 patients (1.5%) receiving empagliflozin compared with 60 of 2323 (2.6%) in the placebo group, representing a relative risk reduction of 44% (HR for empagliflozin, 0.56; 95% CI, 0.39-0.79; P <.001).

Furthermore, the EMPA-REG OUTCOME analysis demonstrated additional reductions in the need for renal replacement therapy initiation (13 of 4687 patients [0.3%] receiving empagliflozin vs 14 of 2333 [0.6%] receiving placebo; relative risk reduction, 55%), though renal disease led to more deaths in the empagliflozin arm (3 in the empagliflozin group [0.1%] vs none in the placebo group, [0.0%]).[7] Results of this analysis have suggested beneficial renal outcomes attributed to treatment with empagliflozin, independent of cardiovascular risk reduction.

Investigators have also evaluated renal outcomes associated with dapagliflozin therapy in a post hoc pooled analysis of 2 phase 3 clinical trials in patients with type 2 diabetes and uncontrolled hypertension.[8] The analysis included data from 356 patients (dapagliflozin, n = 167; placebo, n = 189) with microalbuminuria or macroalbuminuria at baseline. Patients randomized to receive dapagliflozin experienced a greater reduction in albuminuria at 12 weeks, based on urine albumin/creatinine ratio, compared with those receiving placebo (absolute difference, –33.2%; 95% CI, –45.4 to –18.2). Investigators also observed a decrease in estimated glomerular filtration rate (eGFR) in patients receiving dapagliflozin (–2.80 mL/min/1.73 m^2 at 12-week follow-up; 95% CI, –5.43 to –0.16), which was reversed after stopping therapy.[8]

Whether the reduction in renal outcomes is a class-wide effect remains unknown, so the presentation of key findings and data analysis from the CREDENCE trial were a highlight of the 79th Scientific Sessions. This is the first randomized, prospective, double-blind, placebo-controlled, multicenter, parallel-group trial specifically powered to evaluate the effects of canagliflozin on major renal outcomes. Its primary end point is time to first occurrence of any event in the primary composite end point (end-stage kidney disease, doubling of serum creatinine, renal or cardiovascular death) in patients with diabetes, CKD (defined as an eGFR of 30 to less than 90 mL/min/1.73 m^2), and macroalbuminuria, who are receiving a maximally tolerated angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.[9] The recent publication of the CREDENCE findings has shed light on these potential benefits and, importantly, helped to show that these benefits may represent a class-wide effect. Notably, the CREDENCE trial was concluded after an interim analysis, as its prespecified efficacy objectives had been met. Patients treated with canagliflozin had an average event reduction of 30% for the composite primary end point, and from a safety perspective, CREDENCE did not identify a higher risk of fractures or amputation in the canagliflozin group. The risk of diabetic ketoacidosis was significantly higher in patients treated with canagliflozin compared with placebo (2.2 vs 0.2 events per 1000 patient-years, respectively), though this is not a surprising finding for an SGLT2 inhibitor.[10]

Investigators also presented the results from the CARMELINA trial, published earlier this year, at the 79th Scientific Sessions. The major study evaluated the effect of linagliptin compared with placebo on the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in patients with elevated baseline cardiovascular and renal risk. Background standard-of-care diabetes management was offered to the 6979 patients in both treatment arms (linagliptin, n = 3494; placebo, n = 3485), though the use of DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists was disallowed via predefined exclusion criteria. For the 3-point MACE primary outcome, linagliptin (12.4%) was shown to be noninferior to placebo (12.1%) groups (HR, 1.02; 95% CI, 0.89-1.17; P <.001 for noninferiority). Subsequent testing for superiority for this primary outcome was not statistically significant (P = 0.74). Similarly, the secondary composite outcome of time to first occurrence of end-stage renal disease, death due to renal failure, or sustained decrease in eGFR by 40% from baseline was not statistically

different between the linagliptin (9.4%) and placebo (8.8%) groups (HR, 1.04; 95% CI, 0.89-1.22; $P = 0.62$).[11] Although some exploratory outcomes of CARMELINA showed promise (eg, reduction in albuminuria progression) in the linagliptin arm, the overall results are not likely practice changing to the same degree as the cardiovascular and renal outcomes trials conducted with other pharmacotherapy options in other antidiabetic drug classes.

Beyond these trials, several additional study announcements included the role of vitamin D in diabetes prevention, the role of lifestyle intervention in preventing diabetes, the possible use of SGLT2 inhibitors in managing type 1 diabetes, and the efficacy and safety of an oral semaglutide formulation. Further, additional safety data are necessary to inform and elucidate risks associated with both drug classes (euglycemic diabetic ketoacidosis and amputation risk with SGLT2 inhibitor use and cancer risks associated with GLP-1 receptor agonists and DPP-4 inhibitors) and provide clarification on risk factors associated with these specific adverse events. In the meantime, the growing body of outcomes data related to cardiovascular and, now, renal outcomes has begun to shed some light on the potential role of multiple pharmacotherapy options in the individualized management of diabetic patients. ◆

AUTHOR INFORMATION

Joseph Cruz, PharmD, BCPS, a graduate of the Ernest Mario School of Pharmacy (EMSOP) at Rutgers University, completed an American Society of Health-System Pharmacists–accredited PGY-1 pharmacy residency and a PGY-2 drug information specialty residency at Robert Wood Johnson University Hospital.

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INDUSTRY PERSPECTIVE

AstraZeneca's Khan Discusses Dapagliflozin and Cardiovascular, Renal Outcomes in Diabetes Care

Mary Caffrey

continued from cover

KHAN

Naeem Khan, MD, vice president of US cardiovascular and metabolic diseases, AstraZeneca.

dedicated renal outcomes trial reported results in April,[3] and more are on the way. (Upcoming dedicated trials also will examine the effects of SGLT2 inhibitors on heart failure.)

Finding ways to prevent the loss of renal function, including the need for dialysis, is a priority of managed care. Doing so would not only improve quality of life for patients but also bring savings for Medicare—the annual cost of a year of dialysis is estimated at $89,000.[4]

Evidence-Based Diabetes Management™ (*EBDM*) asked **Naeem Khan MD,** vice president of US cardiovascular and metabolic diseases at AstraZeneca, to discuss lessons from the CVOTs, the new focus on renal outcomes, and what's next for SGLT2 inhibitors.

***EBDM*: As a class, SGLT2 inhibitors are proving to have many benefits beyond lowering blood glucose for patients with T2D. For the past 4 years, much of the focus at major scientific meetings has been on CVOT results—reduction in major cardiovascular events. But those results also contained evidence that the class also had the ability to play a major role in preventing the slow progression to debilitating conditions like kidney failure. Can you discuss why the renal benefits of SGLT2 inhibitors are getting more attention now?**

KHAN: The primary focus of cardiovascular safety and the reduction in major cardiovascular events by SGLT2 inhibitors stems from cardiovascular outcomes trials that were mandated following the 2008 guidance from the FDA to confirm these medicines were safe from a cardiovascular perspective.[1] With this in mind, it's easy to see why confirming the CV safety and efficacy of these medicines was established as the primary objectives of these trials and therefore were the first topics of scientific discussion.

We have always known that patients with diabetes have an increased risk of renal complications. In fact, diabetes is the leading cause of kidney disease, and approximately 1 in 4 adults with diabetes has kidney disease.[5] Although the initial SGLT2 inhibitor CVOTs were focused on CV outcomes, secondary analyses were included to assess renal impact. These secondary analyses generated interesting hypotheses about SGLT2s and their impact on renal outcomes. As a result of these findings, AstraZeneca is prospectively evaluating these hypotheses in a large randomized clinical trial known as Dapa-CKD,[6] a study evaluating the effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease (CKD).

***EBDM*: Can you discuss the new indication that dapagliflozin received from the FDA and why this is important?**

KHAN: The FDA approved an updated label for Farxiga that expands who may benefit from the medicine—specifically, for patients with T2D and moderate renal impairment [CKD with an estimated glomerular filtration rate (eGFR) of 45-59 mL/min/1.73 m^2.[7] The updated label lowers the eGFR threshold to 45 mL/min/1.73 m^2 from 60 mL/min/1.73 m^2]. Because patients may be affected by metabolic and renal complications that are interrelated, it's important to have information about how these medicines work in patients with both conditions included in the prescribing information for [dapagliflozin].

***EBDM*: When the first CVOT, EMPA-REG OUTCOME,[8] was announced, AstraZeneca added a primary end point to its CVOT, the DECLARE-TIMI trial, which has reported results at meetings for the American Heart Association and American College of Cardiology. Can you discuss this decision and the importance of this additional primary end point?**

KHAN: Every time you conduct a clinical trial, you ask a specific question and receive an answer, but each trial also generates new hypotheses and therefore questions that need to be answered by a subsequent clinical trial. The benefit of being the third CVOT is that we were able to take some of the questions generated by the results of the other CVOTs and prospectively study them in DECLARE. In DECLARE, the study design was adjusted to include coprimary end points of MACE as well as the composite of hospitalization for heart failure or CV death, because we believed understanding the impact on hospitalizations for heart failure would be especially important—particularly because 1 out of every 3 patients with diabetes will go on to have heart failure, heart failure is the first cardiac complication for most patients, and the mortality rates for heart failure are quite high.

> **"The benefit of being the third CVOT [cardiovascular outcomes trial] is that we were able to take some of the questions generated by the results of the other CVOTs and prospectively study them in DECLARE."**
>
> — Naeem Khan, MD

With more than 17,000 patients in 33 counties, DECLARE provides a broad representation of type 2 diabetes patients with cardiovascular risk factors and established cardiovascular disease, offers a rich body of scientific evidence for this patient population, and the benefit was seen in the broadest patient population to date, making it highly relevant to the real-world clinical setting.

[Note: DAPA-HF,[9] the first trial evaluating the effect of an SGLT2 inhibitor on the incidence of worsening heart failure or cardiovascular death in patients with chronic heart failure and with and without T2D, is expected to read out this year.]

INDUSTRY PERSPECTIVE

***EBDM*: What is the significance of the American Diabetes Association (ADA) releasing a midyear guideline update to include new evidence on dapagliflozin?**[10]

KHAN: The addition of new data that feature the most up-to-date research on CV and renal risk reduction in patients with type 2 diabetes for the SGLT2 inhibitor class in the ADA *Standards of Care* [*Standards of Medical Care in Diabetes*] helps empower healthcare professionals to provide evidence-based care to their patients and help improve outcomes. Heart failure is the No. 1 cardiac complication in patients with type 2 diabetes.

***EBDM*: We just had the first of the new wave of reported results from renal outcomes trials, and Dapa-CKD will be complete in 2020. Significantly, half of these patients do not have diabetes. Is there anything you can tell us about the study so far?**

KHAN: The Dapa-CKD trial is designed to evaluate the effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with CKD and includes both patients with and without type 2 diabetes. It is a randomized, multicenter, event-driven, double-blind, placebo-controlled study involving 4000 patients with CKD. The primary outcome is defined as the composite of time to first occurrence of ≥50% sustained decline in eGFR, reaching end stage renal disease (ESRD) or CV death or renal death. ESRD is defined as sustained eGFR <15 mL/min/1.73m^2, chronic dialysis treatment or receiving a renal transplant.

Dapa-CKD is expected to read out in 2020.

***EBDM*: Given the extreme burdens for patients, high mortality rates for those who begin dialysis, the diminished quality of life, and the cost to Medicare, how do the potential renal benefits of SGLT2 inhibitors compare with the CV benefits?**

KHAN: It is probably too early to make a definitive statement about this. What we know is that the risk of developing renal impairment or CKD is high among patients with diabetes, and the SGLT2 class of medicines has generated some interesting and promising hypotheses about how they may affect the kidney. As we continue to evaluate the potential benefits of SGLT2 inhibitors, we believe these treatments could become innovative options that may address cardiorenal risks for patients with diabetes. ◆

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CLINICAL TRIAL

CREDENCE: First Renal Outcomes Trial Finds Canagliflozin Cuts Risk of Renal Failure, Death; Prompts ADA Updates

Mary Caffrey

MAHAFFEY

Kenneth Mahaffey, MD, professor of medicine, Stanford University Medical Center.

continued from cover

canagliflozin cut the risk of renal failure or death by 30% in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD).[2] These results, unveiled at the International Society of Nephrology 2019 World Congress of Nephrology in Melbourne, Australia, were simultaneously reported in the *New England Journal of Medicine*.[2]

Canagliflozin is sold as Invokana by Janssen Pharmaceutical Companies of Johnson and Johnson.

The findings prompted the American Diabetes Association (ADA) to update its *Standards of Medical Care in Diabetes* on June 3, 2019,[3] in 2 chapters that deal with cardiovascular (CV) disease and risk management[4] and microvascular complications and foot care.[5]

Then, on June 11, 2019, during the Scientific Sessions in San Francisco, California, CREDENCE coprincipal investigator Kenneth Mahaffey, MD, of Stanford University Medical Center, shared additional data on what the results mean for primary and secondary prevention—namely, how well canagliflozin prevented renal decline in individuals with T2D who had been diagnosed with CV disease or had experienced an event (secondary prevention) as well as those who had neither (primary prevention).[6]

After a series of CV outcomes trials (CVOTS) showed a class effect for CV benefits for SGLT2 inhibitors,[7-9] there was plenty of interest at the 79th Scientific Sessions not only for CREDENCE, but also for secondary findings on renal outcomes from the CVOTS for rival drugs. Other manufacturers have their own dedicated renal outcomes trials in process: AstraZeneca has Dapa-CKD for dapagliflozin (Farxiga),[10] due to report in November 2020, and Boehringer Ingelheim and Eli Lilly have sponsored EMPA-KIDNEY for empagliflozin (Jardiance), due to report in June 2022.[11] Various dedicated trials exploring the therapeutic value of SGLT2 inhibitors in heart failure for patients with and without diabetes are also under way.[12]

SGLT2 inhibitors lower blood glucose by targeting a protein that affects reuptake of glucose by the kidneys back into the bloodstream. Patients who take these drugs excrete glucose out of the body through the urine, and this unique system for discharging extra blood glucose accounts for the drugs' protective effects on the renal system. As described by Christoph Wanner, MD, in a 2017 article, "The potential mechanisms responsible are likely multifactorial, and direct renovascular and hemodynamic effects are postulated to play a central role."[13]

Although an early completion date of CREDENCE had suggested positive results,[14] the magnitude of the benefit surprised some. While moderating a press briefing at the 79th Scientific Sessions, Robert H. Eckel, MD, of the University of Colorado, exclaimed, "CREDENCE—that just knocks your socks off, doesn't it?"

Initial Findings Show No Amputation Risk

Phase 3 results reported in Melbourne show that CREDENCE easily achieved its primary end point; compared with placebo, canagliflozin reduced a composite of (1) the progression to end-stage renal disease (ESRD), defined as the need for chronic dialysis or renal transplant; (2) doubling of serum creatinine; and (3) renal or CV death.[2] This was not unexpected, given the June 2018 announcement that the trial was ending early after independent evaluators determined the primary end point had been met.[14]

CREDENCE did not show the elevated risk of lower extremity amputation seen in CANVAS,[8] the CVOT for canagliflozin that caused the FDA to issue a boxed warning, even though the same trial found benefits that led to an indication for lower risk of CV events.[15] When asked if these results would prompt the drug maker to seek removal of the warning, Janssen officials said in an email that the new data are "reassuring" because they "show no imbalance" in either fractures or amputations between the canagliflozin or placebo arms; the company will be working with the FDA, "to reflect these safety findings in the Invokana label."

Janssen is seeking an additional indication for canagliflozin, based on the CREDENCE findings.[16]

CREDENCE was a double-blind trial that randomized 4401 patients with a median follow-up of 2.62 years. Patients had a mean age of 63 years (± 9.2 years) and had lived with T2D for an average of 15.8 years (± 8.6 years). All patients had an estimated glomerular filtration rate (eGFR) of 30 to <90 mL per minute per 1.73 m^2 of body surface area and albuminuria. All were being treated with standard of care, renin-angiotensin system blockade.

Findings included[2]:

- The relative risk (RR) of the primary outcome was 30% lower for those taking 100 mg of canagliflozin compared with placebo; event rates were 43.2 and 61.2 per 1000 patient-years (hazard ratio [HR], 0.70; 95% CI, 0.59-0.82; $P = .00001$).
- The RR for the renal-specific elements of the primary end point—excluding CV death—was 34% lower for those taking canagliflozin (HR, 0.66; 95% CI, 0.53-0.81; $P < .001$).
- The RR of ESRD was 32% lower for those taking canagliflozin (HR, 0.68; 95% CI, 0.54-0.86; $P = .002$).
- Among secondary end points, the risks of CV death, myocardial infarction, or stroke (HR, 0.80; 95% CI, 0.67-0.95; $P = .01$) and for hospitalization for heart failure (HR, 0.61; 95% CI, 0.47-0.80; $P < .001$) was lower among those taking canagliflozin. The authors wrote that these measures may have been limited when the trial ended early, but they were consistent with other randomized controlled trials and real-world studies in SGLT2 inhibitors.

No significant differences were seen in rates of amputations or fractures. In amputation, the HR was 1.11 (95% CI, 0.79-1.56) and in adjudicated fractures, the HR was 0.98 (95% CI, 0.70-1.37). Lower limb amputation rates were 12.3 for canagliflozin versus 11.2 for placebo per 1000 patient-years.

There has been much speculation about whether the amputation findings in CANVAS were due to the makeup of the study population. Authors in CREDENCE wrote that the population in this trial was at high risk for CV events, and they discussed the disparity from the CANVAS findings.

"Whether the increased risk of lower limb amputation in the

CANVAS Program was due to differing trial populations or protocols or to chance remains unclear," they wrote. "The overall safety profile in our trial is otherwise consistent with the known adverse effects associated with canagliflozin."[2]

A Breakthrough With Potential Savings to the Health System

"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," the study's lead author, Vlado Perkovic, MBBS, PhD, FASN, FRACP, said in a statement.[17]

Perkovic, who is cochair of the CREDENCE Steering Committee and executive director of The George Institute for Global Health, Australia, said, "These impressive results from the CREDENCE study have significant clinical implications for preventing kidney failure and improving health for millions of people living with chronic kidney disease and type 2 diabetes."

Researchers and physicians familiar with the CREDENCE trial have hinted as far back as the summer of 2017 that the renal outcomes suggested in CANVAS-R (the renal component of CANVAS) would be fully demonstrated in these results.[18] With T2D being the top cause of kidney failure, a treatment to prevent patients with T2D from needing dialysis or transplant would potentially save millions of dollars for Medicare. A 2018 report from the US Renal Data System (USRDS) found that 1% of the patients in Medicare have ESRD, but they account for 7% of Medicare fee-for-service costs.[19]

When the first CVOT, EMPA-REG OUTCOME,[7] reported that empagliflozin reduced the risk of CV death in 2015, it "changed the landscape in diabetes management," as Julie R. Ingelfinger, MD, and Clifford J. Rosen, MD, wrote in their editorial that accompanied publication of the study.[20] EMPA-REG and subsequent CVOTs showed that SGLT2 inhibitors reduced the risk of hospitalization for heart failure, suggesting that the drugs were not only beneficial to patients, but could also reduce one of the high-cost items in healthcare, just as health systems were being graded on their ability to avoid repeat hospitalizations for this condition.

SGLT2 inhibitors have been shown to reduce hypertension and promote modest weight loss. Existing evidence showing prevention of renal decline last month prompted the American College of Cardiology and the American Heart Association to include the class, with glucagon-like peptide-1 receptor agonists, in an updated primary prevention guideline.[21] Ingelfinger and Rosen wrote that, although several T2D medications show benefits beyond lowering blood glucose, "the SGLT2 inhibitors appear to be the most promising."[20]

CREDENCE shows that canagliflozin has the potential to achieve savings in an area of huge importance to policy makers. Few items tax the health system as much as ESRD, which affects 750,000 individuals in the United States. The USRDS estimates the cost of a year of dialysis at $89,000 per patient[19], and, as Ingelfinger and Rosen wrote, the ranks in need of dialysis and kidney transplants are growing due to rising levels of obesity.[20] They noted that the investigators estimate that among 1000 patients treated over 2.5 years, 21 would need to be treated with canagliflozin to avoid dialysis or transplant, doubling the serum creatinine level, or renal or CV death.[2]

Dialysis and kidney transplant care are so costly that patients with CKD who reach this stage automatically qualify for Medicare at any age; most Medicare Advantage plans do not accommodate these patients unless they have a special needs plan that handles ESRD.[22]

However, the CREDENCE investigators noted that they did not study patients who already had advanced CKD at baseline, or kidney disease believed to have been caused by conditions other than T2D.

Evidence in Both Primary, Secondary Prevention

At the 79th Scientific Sessions, Mahaffey presented a series of slides during a symposium that included the CREDENCE results showing CV and renal outcomes for patients with and without existing CV disease, based on screening the patients at the start of the trial. Those in the secondary prevention group had a history of coronary, cerebrovascular, or peripheral vascular disease, procedures, or events.[6,23]

The primary prevention group had 49.6% of the participants, was younger, and had more women, but had similar measures of glycated hemoglobin and low-density lipoprotein cholesterol. As expected, the secondary prevention group began the trial with higher rates of hypertension, heart failure, CV disease, peripheral vascular disease, and amputations. The 2 groups had similar duration of T2D and level of renal function, according to Mahaffey's presentation.[23]

Overall, the data Mahaffey shared showed that canagliflozin demonstrated "important reductions in CV death and hospitalization for heart failure," in both the primary and secondary prevention groups:[23] There was a 26% reduction in hazard of CV death or hospitalization for heart failure in the primary prevention group.

There was a 34% reduction in the hazard of CV death or hospitalization for heart failure in the secondary prevention group.

For the combined end point of CV death, myocardial infarction or stroke, there was a 32% reduction in the primary prevention group, and a 15% reduction in the secondary prevention group.

For CV death, Mahaffey said there were "very similar" HRs, translating into a 25% reduction in the primary prevention group and a 21% reduction in the secondary prevention group.

"These data show, for the first time, important reductions in these end points with an agent to treat [T2D] and [CKD] in both primary and secondary prevention groups," Mahaffey said.

Data showed similar results for the composite renal end point between the primary and secondary prevention groups, "very different from the [CV] results," he said.

In a statement, Mahaffey said the new analysis shows that canagliflozin can manage serious complications from T2D, including CV and kidney disease. "We're particularly excited about this new analysis, because it's the first time a [T2D] medicine has shown a [CV] benefit in patients who did not have pre-existing CV disease. This is an important, clinically meaningful finding as it uncovers the potential of canagliflozin to offer a protective effect in this patient population."[24] ◆

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Highlighting Links Between Kidney, CV Disease in Diabetes

Mary Caffrey

FROM SESSIONS ON TREATMENT choices for cardiorenal protection, to clinical trials on cardiovascular and renal outcomes, to the choice of a leading researcher in diabetes and renal care to deliver the annual Bierman Lecture, it was hard to miss the theme of cardiorenal care at the 79th Scientific Sessions of the American Diabetes Association (ADA) in San Francisco, California.

Researchers have known for years that people with diabetes face a higher cardiovascular risk. They are up to 4 times more likely to die from heart disease.[1] It is also well known that diabetes is linked to kidney failure[2]; about 30% of those with type 1 diabetes and 10% to 40% with type 2 diabetes (T2D) will progress to this stage.

But as Peter Rossing, MD, DMSc, of the Steno Diabetes Center in Copenhagen, Denmark, said June 10, 2019, after accepting the Edwin Bierman Award,[3] more work is being done to understand the functional links between chronic kidney disease (CKD) and cardiovascular disease and how to treat them.

"Diabetes, cardiovascular disease, and renal disease—that's an unfortunate triad," he said. CKD, in particular, "is a disease multiplier" because of its effect on life expectancy. A 30-year-old with diabetes and CKD can expect to lose 15 to 16 years of life due to the complications, Rossing said.

This work is informing guidelines for clinical care, he added. This year, the ADA issued guideline updates based on results from 2 trials—DECLARE[4] for dapagliflozin and CREDENCE[5] for canagliflozin—with the most recent revision coming June 3.[6,7]

The wave of cardiovascular outcomes trials for sodium glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists produced secondary outcomes that show these classes have cardiorenal benefits; drugs in the SGLT2 class, in particular, are now being studied in dedicated renal outcomes trials, with CREDENCE producing the first results in April 2019 (see **Cover** story).

Mechanisms for these findings were not understood at first, Rossing said. "How can it be that these glucose-lowering agents protect the kidney and the heart? It must not be about glucose—it must be about something else."

And it is likely that lowering uric acid and volume contribute to these results, he added.

Whatever the reason, having new options is important, Rossing said, because data show relying on lifestyle changes alone for people with diabetes to reach targets in glycated hemoglobin, blood pressure, and cholesterol won't work.

Both in the Bierman Lecture and at length on June 9, 2019, during a session between the ADA and the American Society of Nephrology (ASN), Rossing discussed work on blocking the hormone aldosterone, given the increased understanding of its role as an independent facilitator of kidney damage. He called attention to 2 ongoing trials, FIDELIO[8] and FIGARO,[9] that are investigating, respectively, whether the compound finerenone can reduce (1) the progression of kidney disease and (2) cardiovascular mortality and morbidity in patients with T2D and diabetic kidney disease.

Rossing also discussed the importance of biomarkers. "Many of the markers in kidney disease are also good markers in cardiovascular disease," he said.

He discussed the roles of inflammation, oxidative stress, uric acid, and new work that could signal gut microbiota as a potential treatment target.[10] Studies of adipose tissue are revealing inflammatory markers, Rossing said, but "I think we need a lot more data in this area to know how to use adipose tissue as a marker or target."

On the horizon, Rossing is working on the PROMINENT trial, which is looking at pemafibrate to treat triglycerides and reduce cardiovascular events.[11]

Precision Medicine in Diabetes and Kidney Disease

Also at the ADA/ASN joint session, Alice Cheng, MD, FRCPC, of the University of Toronto, said that diabetes medicine took a one-size-fits-all approach for many years. As recently as 2009, the guidelines had minimal options: metformin, basal insulin, sulfonylureas, and intensive insulin.[12]

Now there are multiple options and physicians can be more precise, she said. Diabetes is not where oncology is in the use of biomarkers to match treatments with patients based on individual characteristics, she said, but it's moving in that direction.

More work on the genetics of diabetes is allowing researchers to home in on variables such as insulin deficiency, insulin resistance, or whether diabetes is obesity related or age related.

"In diabetic kidney disease, this is clearly an area of interest," Cheng said. The use of biomarkers and data integration will eventually allow better risk stratification—and when drugs are tested, researchers will be able to "identify those who will respond the best."

She outlined how work by the Berthier research group led to findings about the role of JAK1/JAK2 inflammation in the progression of kidney disease and how that led to phase 2 findings that JAK1/JAK2 inhibition with baricitinib decreased albuminuria in patients with T2D and diabetic kidney disease.[13]

This kind of work involves the "omics," as in the proteomics, genomics, and more—and there may be more than one pathway toward a target, depending on the patient. It all starts with tissue, which Cheng said this is a key issue. Although study results show patients are willing to share blood and tissue samples to create data banks, they have some concerns and many want results back.

In the future, clinical trial designs may look very different based on this type of work, she said. "There will be many therapeutic options in the future," and when considering the needs of an individual, "We want to capture the diagnostics and patient preferences, of course, and ultimately fit the right drug for the right stage."

"We really require early engagement of stakeholders for this to be successful," she said.

Inflammation in Kidney Disease

Also at the ADA/ASN session, Aruna Pradhan, MD, MPH, MSc, of Harvard and Brigham and Women's Hospital, discussed the CANTOS trial[14] for canakinumab in atherosclerotic cardiovascular disease and asked, "What does the CANTOS trial tell us about inflammation and diabetes risk—and these 2 connected pathways?"

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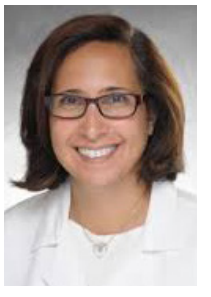

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Pradhan talked about the role of C-reactive protein (CRP), a blood test marker for inflammation in the body. "Inflammation is a consistent predictor a year before one develops a myocardial infarction," she said, so the thinking was that treating patients with a history of high CRP would prevent events.

Inflammation as a marker, especially for patients with CKD, turned out to be extremely important. Among patients in CANTOS with CKD (estimated glomerular filtration rate <60 cc/min/1.73 m^2), major adverse vascular events dropped 18% among those taking canakinumab; the benefits were greatest among those whose CRP was greatly reduced.[15]

"Independent of other risk factors, these data suggest the signal is real," she said.

Those with high CRP and high levels of low-density lipoprotein cholesterol had the worst outcomes, so Pradhan suggests a dual therapy to treat both conditions is needed.

Understanding the Role of Uric Acid

Diana Jalal, MD, a nephrologist at the University of Iowa, concluded the ADA/ASN session by discussing conflicting results from trials involving uric acid. High levels of uric acid are seen in kidney disease, and hyperuricemia is linked to both cardiovascular and kidney disease, with strong associations with heart failure and obesity.

"The data do suggest a link between hyperuricemia and outcomes in patients with diabetes and chronic kidney disease," she said. Thus, lowering uric acid may improve outcomes.

However, Jalal reviewed trials and found that studies with results that showed lowering uric acid led to better outcomes were not adequately powered and could not be replicated. "None were designed to evaluate hard outcomes in patients with CKD and type 2 diabetes."

More work is needed to understand whether the elevation of uric acid "is a manifestation of disease," she said. ◆

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CARMELINA Results in Linagliptin Show Neutral Renal Outcomes in Elderly Patients

AJMC Staff

A SYMPOSIUM ON RENAL outcomes in type 2 diabetes (T2D) therapies held June 11, 2019, at the 79th Scientific Sessions of the American Diabetes Association (ADA) featured results from CARMELINA,[1] a study that evaluated the effect of linagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, on cardiovascular and kidney safety. During a press briefing ahead of the program, investigators emphasized that patients with T2D and kidney disease have received less attention in trials of DPP-4 inhibitors.

Results showed, compared with placebo, there was no significant difference in the 3-part major adverse cardiovascular events (MACE) and neutral findings for renal outcomes in elderly patients.

Before results for CARMELINA were presented, Boehringer Ingelheim and Eli Lilly, which market linagliptin as Tradjenta, announced results for CAROLINA,[2] which compared linagliptin with glimepiride, a second-generation sulfonylurea. Officials touted CAROLINA as "the only active comparator outcome trial" for a DPP-4 inhibitor, with the results showing that linagliptin was not inferior to glimepiride in the first occurrence of 3-part MACE and similar in a secondary end point of 3-part MACE plus hospitalization for unstable angina.

More patients taking linagliptin achieved a second composite outcome of reaching a glycated hemoglobin level of 7% without a rescue medication, moderate or severe hypoglycemia, or 2% weight gain.

When asked during a press briefing where DPP-4 inhibitors generally and linagliptin specifically fit in among T2D therapies, investigator Julio Rosenstock, MD, director of the Dallas Diabetes Research Center, said the results from CARMELINA show that linagliptin is safe to use for older patients who need help with glycemic control. "We can state with a great deal of confidence that using a DPP-4, including linagliptin, is safe from a cardiovascular point of view and safe if they have kidney disease—and safe in older people," he said. "That's my take-home message." ◆

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DECLARE Shows Dapagliflozin Prevented Renal Decline in T2D, Even for Those With Good Kidney Health

Mary Caffrey

DATA FROM THE DECLARE–TIMI 58 study, the cardiovascular outcomes trial (CVOT) for dapagliflozin (Farxiga), reveal that the type 2 diabetes (T2D) drug significantly reduced the risk of renal decline, kidney failure, and renal death, according to results presented June 9, 2019.[1]

Findings, reported at the 79th Scientific Sessions of the American Diabetes Association (ADA), held in San Francisco, California, and published simultaneously in *Lancet Diabetes & Endocrinology* show that treatment with the sodium glucose cotransporter 2 (SGLT2) inhibitor made a difference even for those in good renal health when the study began. The study authors noted this point, because a dedicated renal outcomes trial for dapagliflozin is forthcoming.[2]

"The effect of SGLT2 inhibitors on nephropathy is being examined in dedicated studies of renal outcomes, both in patients with and without type 2 diabetes," wrote the study authors, led by Ofri Mosenzon, MD, of Hadassah Hebrew University Hospital in Jerusalem. "However, these trials focus on populations with nephropathy at baseline, and therefore should be considered as complementary to our findings."[1]

The need for better solutions to prevent renal decline in diabetes—and the apparent ability of SGLT2 inhibitors to offer options—were a major focus of the Scientific Sessions. Diabetes, cardiovascular disease, and chronic kidney disease (CKD) often occur together, and having 1 condition increases the risk of developing the others, along with other comorbidities; for this reason, CKD is often called a "disease multiplier."[3] Those with CKD are at least 6 times more likely to develop end-stage renal disease (ESRD), one of the most debilitating conditions for patients and one of the costliest for the health system.[4]

"The effect of SGLT2 inhibitors on nephropathy is being examined in dedicated studies of renal outcomes, both in patients with and without type 2 diabetes. However, these trials focus on populations with nephropathy at baseline, and therefore should be considered as complimentary to our findings."

— Lancet Diabetes & Endocrinology

The cost of dialysis per patient is estimated at $89,000 per year; patients who reach this point automatically qualify for Medicare. Estimates show that 750,000 people in the United States have ESRD, and this number has been projected to increase due to the rising rate of obesity.[5]

Like other CVOTs, DECLARE was required to demonstrate safety under a 2008 FDA guidance. Investigators expanded the trial to include hospitalization for heart failure as a second primary end point, after the 2015 EMPA-REG OUTCOME trial unexpectedly showed that the SGLT2 inhibitor empagliflozin reduced cardiovascular death by 38% and hospitalization for heart failure by 35%.[6]

Thus, DECLARE is the only trial for an SGLT2 inhibitor to report reduced hospitalization for heart failure and cardiovascular death as a primary end point.[7]

DECLARE investigators previously presented findings at the American Heart Association meeting in November 2018[7] and the American College of Cardiology (ACC) Scientific Session in March, focusing on the drug's ability to prevent complications from heart failure.[8]

Taken together, the results hold much promise, according to Kiersten Combs, vice president for US cardiovascular and metabolic disease for AstraZeneca, the maker of dapagliflozin. "We're almost at a turning point here in treating the diabetic patient and their comorbidities or complications," Combs said in an interview with *The American Journal of Managed Care®* (*AJMC®*).

In the past, the conversation with health systems has been about how well a T2D therapy controlled blood glucose levels, but the growing body of evidence for cardiorenal results generates a broader conversation, said Naeem Khan MD, vice president of medical for US Cardiovascular and Metabolic Diseases at AstraZeneca, in the interview with *AJMC®*. "Now the evidence has brought us to a point where we say [that] diabetes is a risk factor that affects other vital organs, and the organs are the heart and the kidney," Khan said.

The DECLARE data had already produced a primary end point showing that dapagliflozin reduced hospitalization for heart failure and cardiovascular death, Khan said, and now the data show benefits for the renal system. Given the grim trajectory for patients with diabetes who develop cardiovascular disease and CKD, the results "change the whole paradigm," he said.

"What you're seeing, which is so exciting, with the SGLT2 class—and with Farxiga specifically, with DECLARE—is this body of evidence around how treating beyond the A1C [glycated hemoglobin] improves these patients' quality of life and slows not only the diabetes [but also] the disease that the diabetes can exacerbate," Combs said.

These latest results are from a prespecified exploratory analysis of renal-only outcomes, examining results from 17,160 patients with T2D and mostly preserved renal function, regardless of underlying atherosclerotic cardiovascular disease. Follow-up was 4.2 years.[1]

Last November, investigators reported a 24% decline in a composite of cardiorenal measures for patients taking dapagliflozin.[7] At the 79th Scientific Sessions, they reported that patients taking dapagliflozin had a 47% reduction compared with placebo in the relative risk of a composite renal outcome, which included kidney function decline, defined as sustained ≥40% decrease in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73m^2; ESRD; and renal death. The difference was 1.5% versus 2.8%; (hazard ratio [HR], 0.53; 95% CI, 0.43-0.66; $P = .0001$).[1]

This result was driven by a 46% reduction in kidney function decline, as there were relatively few incidents of ESRD or renal death: 11 (0.1%) in the dapagliflozin group compared with 27 (0.3%) in the placebo group. The authors noted that preservation of renal function with dapagliflozin was seen across subgroups. Although there was a decline in eGFR in the dapagliflozin group relative to placebo after 6 months, this difference was eliminated after 2 years; at years 3 and 4, the mean decrease in eGFR was less with dapagliflozin.

"In both aspects, when you look at the renal by itself or the cardiorenal, you see great benefit when you [use] Farxiga in this patient population," Khan said. "That's not only the people with established cardiovascular disease but also the people with multiple risk factors. And that's the kind of patient population the physician actually sees in the office."

Khan pointed out that most study participants had good renal health at baseline, yet taking dapagliflozin made a significant difference in their long-term outcomes. Of the group, 47.6% had a baseline eGFR of at least

continued

90 mL/min/1.73m^2, which is normal renal function, and another 45.1% had an eGFR of 60 to <90 mL/min/1.73m^2.

"These are results we saw in a broad range of patient population that actually had a mean eGFR of 85 [mL/min/1.73m^2]. That's quite a healthy kidney, and yet we saw these benefits," Khan said. "This is stage 1 [CKD] and earlier," he added.

"It's very impactful to look at how healthy the kidney was when they were getting the treatment," Khan said. This points to how much damage diabetes can do to the renal system in a relatively short period.

As CVOTs for the SGLT2 inhibitor class demonstrated the drugs' ability to slow renal decline, makers of these therapies launched dedicated renal outcomes studies. In March, investigators for the first such study, CREDENCE, for canagliflozin, reported a 30% reduction in renal failure or death for patients with T2D and CKD.[9] The renal outcomes study for dapagliflozin, Dapa-CKD, is under way and has an estimated completion of November 2020.[2]

There has been speculation that as SGLT2 inhibitors gain new indications and find their way into guidelines outside of diabetes—the ACC now recommends the class in primary prevention—there will be greater use by patients newly diagnosed with diabetes.

Along with the results for Dapa-HF, a dedicated heart failure trial due to report later this year, this evidence "should give the primary care physician the confidence to treat more aggressively earlier in diabetes," Combs said. The results should also give specialists such as cardiologists the confidence to treat comorbidities seen in patients with diabetes, she said. ◆

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ADA Sessions Offer News on Diabetes Technology

AJMC® *Staff*

THE 79TH SCIENTIFIC SESSIONS of the American Diabetes Association (ADA) offered plenty of news from the technology front—studies about emerging products, as well as updates on those already on the market. ADA included advances in diabetes technology in a special briefing, and there was plenty happening both on and off the exhibit floor. Here is a sample of the news:

Tidepool Announces Key Partnerships With Dexcom, Medtronic

The first day of the 79th Scientific Sessions on June 7, 2019, featured a pair of big announcements from Tidepool: first, that it will create a partnership with Dexcom to integrate Dexcom's G6 interoperable continuous glucose monitoring (CGM) system into the Tidepool Loop—its effort to support the do-it-yourself open-source automated insulin delivery app.[1] Second, that Tidepool will collaborate with Medtronic to develop a Bluetooth-enabled MiniMed insulin pump.[2] Tidepool has an existing relationship with Insulet, maker of the Omnipod. The news came at the annual DiabetesMine D-Data session. In a blog post, Tidepool's president and chief executive officer, Howard Look, updated the diabetes community on efforts to develop an FDA-regulated iOS app for automated insulin delivery.[1]

Medtronic Announces Real-World Data From Guardian Connect and Sugar.IQ

On June 9, 2019, Medtronic presented data at ADA Sessions for its Guardian Connect CGM system and the Sugar.IQ app, which integrates data with that from the Guardian system using artificial intelligence from IBM Watson Health to help those with diabetes stay in their target range.[3] Data from the 3100 individuals who used the app-driven system for at least 5 days showed that they had 4.1% more time in range (63.4%) compared with Guardian alone (59.3%), for a difference of about 1 more hour per day. Each 4% change in time in range helps patients achieve a 0.3% change in glycated hemoglobin (A1C).[3,4]

First Human Tests of Gen3 iLet Bionic Pancreas Presented

The special diabetes technology press briefing featured results for the Gen3 iLet, a bionic pancreas model being developed by Beta Bionics, which is described as a "purpose-built, fully integrated bionic pancreas platform." Developers say it can use either the Dexcom G5 or the Senseonics Eversense implanted CGM. They performed a random, crossover outpatient study that compared the iLet insulin-only mode with usual care for 7 days each, in 17 patients with type 1 diabetes (T1D) from Stanford (using Dexcom G5) and 17 patients with T1D from Massachusetts General Hospital (using Eversense). Researchers monitored the patients remotely and measured mean glucose, time with glucose concentration less than 54 mg/dL, and secondary measures including time in range. There were no differences in time below 54 mg/dL or mean CGM glucose, but iLet increased time in range (70.1% vs 61.5%). No serious adverse events were reported in either arm. Researchers said reports from patients during the study led to improvements in the bionic pancreas.[5]

CITY Reports CGM Helps Teens, Young Adults Reduce A1C

Lori Laffel, MD, MPH, chief of the Pediatric, Adolescent and Young Adult Section at Joslin Diabetes Center, presented results from CITY (CGM Intervention in Teens and Young Adults with Type 1 Diabetes).[6] The study evaluated how the use of CGM affected disease management of 153 teens and young adults aged 14 to 24 years—an age group that Laffel has researched for decades. Historically, this group often sees a drop in glycemic control as parents hand over the reins of disease management. This group did not necessarily embrace earlier generations of CGM, but newer systems require less patient involvement. The study participants were randomized to wear either a Dexcom CGM or use standard blood glucose management practices. Results showed that 70% of the CGM group wore the device an average of 5 days or more per week. After 6 months, less than 10% of the users were no longer wearing the device.[6]

SENCE Finds Fewer Glycemic Extremes With CGM in Youth

A study that looked at how CGM use affected glucose management in young children had mixed results, but offered direction for future training for youth and families with T1D Strategies to Enhance New Continuous Glucose Monitoring Use in Early Childhood (SENCE) enrolled 143 children aged 2 to 7 years who had not previously used a CGM. They were randomly assigned to 3 groups: 1 did self-monitoring of blood glucose with a meter and test strips, 1 used CGM, and 1 used CGM with 5 half-hour education family intervention sessions. Initial results did not show differences in time in range among the groups, but a second look showed the group that received the education sessions had better time in range in the later weeks of the study. Quality of life among CGM users was improved, with families worrying less about diabetes care, and CGM compliance was 90%. Groups using CGM also had fewer episodes of hypoglycemia and hyperglycemia.[7]

Diasome Presents Phase 2B Data on Nanotechnology That Targets Insulin to Liver

A game-changing insulin delivery approach may be on the way. Diasome presented results from a phase 2B clinical trial for its hepatocyte directed vesicle (HDV) technology, which targets insulin directly to the liver and allows users to manage T1D with far less insulin.[8] The additive, which directs insulin with a nanoparticle disc, is designed to work with all commercial insulins and is mixed directly with insulin before administration. In the 26-week ISLE-1 (InSulin Liver Effect) study, patients either had conventional mealtime treatment with insulin lispro alone or insulin lispro with the HDV additive. Results showed that patients with an A1C of 8.5% or greater taking insulin with HDV had the same A1C reduction as those taking insulin without the additive, but took about 25% less bolus insulin and spent 73% less time in hypoglycemia.[9] ◆

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ADA Issues Time-in-Range Targets for CGM Use

Mary Caffrey

AN INTERNATIONAL PANEL HAS called for most users of continuous glucose monitoring (CGM) to keep their blood sugar within target ranges at least 70% of the time, under guidelines presented during the 79th Scientific Sessions of the American Diabetes Association (ADA).

For most CGM users, maintaining blood glucose levels between 70 mg/dL and 180 mg/dL for 16.8 hours per day would keep their glycated hemoglobin (A1C) below 7%, the panel reported in a manuscript, "Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations from the International Consensus on Time in Range." The paper appeared online in *Diabetes Care* and its findings were unveiled June 8, 2019, during the 79th Scientific Sessions in San Francisco, California.[1]

Recent leaps in CGM technology include more accurate sensors, hybrid closed loop systems, and factory calibration that frees users from required needle sticks multiple times a day.[2-4] Additionally, the FDA has created a new approval pathway for interoperable CGM systems.[2] Just before the Scientific Sessions began, the FDA approved a dosing indication for Eversense, a model that can be implanted under the skin for up to 3 months.[5] Although more patients are using CGM—it is considered standard of care for type 1 diabetes (T1D)—the panel concluded that "successful utilization of CGM technology in routine clinical practice remains relatively low."[1]

Indeed, data presented by the T1D Exchange show that A1C levels for this group are rising, even though CGM use has climbed from 7% to 30% between 2010-2012 and 2016-2018.[6] A1C levels are generally lower among CGM users, but they are worse for other groups, including teenagers.[6] Authors of the *Diabetes Care* article say that, although peer-reviewed articles have established key metrics for CGM use, formal adoption of guidelines by diabetes professional organizations did not follow—until now.[1]

In recent years, both clinical researchers and advocacy groups have pressed for time in range to gain recognition as a key measure in diabetes care—one that should have consideration alongside A1C as a marker of glycemic control and overall health.[7,8]

The paper's lead author, Tadej Battelino, MD, head of the department of Pediatric and Adolescent Endocrinology at Ljubljana University Medical Centre in Slovenia, described the use of time in range as a complement to A1C in a briefing and statements.[9] But others see time in range as increasingly important and believe it can be used as an end point in short-term studies.[10,11]

Leading diabetes researcher and clinician, Anne L. Peters, MD, professor of Medicine at the Keck School of Medicine at the University of Southern California, went so far as to say that "probably the A1C is a useless number" during a meeting of The Institute for Value-Based Medicine® presented by *The American Journal of Managed Care*® in April 2019. (See **SP240**).

Development of time-in-range guidelines took shape in February 2019 when the Advanced Technologies & Treatments for Diabetes (ATTD) Congress convened an international panel that included physicians, researchers, and individuals living with T1D and type 2 diabetes (T2D). Subgroups formed to review literature and make evidence-based recommendations for each population, which were then presented to the full panel and put to a vote. Modifications to the general recommendations were made for older and high-risk users, as well as those using CGM during pregnancy.

Battelino briefed members of the media on the group's consensus recommendations and encouraged wide dissemination "to improve outcomes and reduce the burden of diabetes." Guidelines[1] are as follows:

T1D/T2D Users

- The target of 70 mg/dL to 180 mg/dL should be maintained at least 70% of the time (16 hours, 48 hours).
- CGM users should allow low blood glucose levels of at least 70 mg/dL for less than 4% of the day (about 1 hour), and very low levels under 54 mg/dL for no more than 1% of the day (15 minutes).
- Users should allow blood glucose levels of more than 180 mg/dL for less than 25% of the time (6 hours), and very high levels of more than 250 mg/dL for less than 5% of the time (1 hour and 15 minutes).

Older/High-Risk Users, Both T1D and T2D

- The target of 70 mg/dL to 180 mg/dL should be maintained more than 50% of the time, or 12 hours.
- Avoiding hypoglycemia is a priority in this population, so CGM users should allow low blood glucose levels under 70 mg/dL for less than 1% of the day (15 minutes).
- Users should allow blood glucose levels of more than 180 mg/dL for less than 50% of the time, and very high levels of more than 250 mg/dL for less than 10% of the time (2 hours, 30 minutes).

Pregnant Users With T1D

- A target of 63 mg/dL to 140 mg/dL should be maintained more than 70% of the time, or 16 hours, 48 minutes.
- Pregnant CGM users with T1D should allow low blood glucose levels under 63 mg/dL for less than 4% of the day (or about 1 hour) and very low levels under 54 mg/dL for less than 1% of the day (15 minutes).
- Users can keep blood glucose of more than 140 mg/dL to less than 25% of the time (6 hours).

Pregnant Users With T2D or Gestational Diabetes

- A target of 63 mg/dL to 140 mg/dL should be maintained.
- The committee declined to give recommendations for percentages of time spent in, below, and above range. This was due to the lack of evidence regarding CGM targets for pregnant women with gestational diabetes or T2D.

How can the guidelines be implemented into clinical practice? The consensus group called for translating the new CGM targets in a standard report, such an ambulatory glucose profile, or AGP Report.

"These standardized CGM metrics and targets will be instrumental in improving care for people with diabetes," Battelino said in a statement.[9] He said that in a clinical practice setting, time in range would prove to be as instrumental to good outcomes as A1C and just as important in making treatment decisions.

Besides the ADA, groups endorsing the report are the American Association of Clinical Endocrinologists, American Association of Diabetes Educators, European Association for the Study of Diabetes, Foundation of European Nurses in Diabetes, International Society for Pediatric and Adolescent Diabetes, JDRF, and Pediatric Endocrine Society. ◆

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Real-World Data Show Patients With T2D Reducing A1C With FreeStyle Libre

Mary Caffrey

NEW REAL-WORLD EVIDENCE SHOWS that patients with type 2 diabetes (T2D) on insulin therapy significantly reduced their glycated hemoglobin (A1C) after 3 to 6 months of using the FreeStyle Libre Flash glucose monitoring system.[1] The findings were presented June 8, 2019, at the 79th Scientific Sessions of the American Diabetes Association meeting in San Francisco, California.

The meta-analysis covered 3 chart review studies involving 363 patient records from Austria, France, and Germany. The average age was 63.5 years (± 11.0 years) and the average time using insulin was 8.3 years (± 5.8 years). Of the group, 56.4% were male. Most had comorbidities, including cardiovascular disease (36.4%), renal complications (33.9%), and retinopathy (19.6%). Besides insulin, 67.8% of the patients were taking oral antidiabetes medications, including metformin, sulfonylureas, sodium-glucose cotransporter 2 inhibitors, dipeptidyl peptidase 4 inhibitors, and thiazolidinediones.

The patients had an average A1C of 8.9% (± 0.9%) and had been on a basal-bolus insulin regimen at least 1 year before starting the FreeStyle Libre system. For the study, A1C was recorded between the 90-day and the 194-day mark after patients began using FreeStyle Libre, between January 2015 and August 2018.

Results showed the following:

After at least 3 months of use, the overall mean change in A1C was reduced by 0.9% ± 0.05% (P <.0001), with no differences between countries.

No significant differences in A1C lowering were seen by age, gender, body mass index, or duration of insulin use.

The FreeStyle Libre system, manufactured by Abbott Diabetes Care Inc, is factory calibrated and does not require finger sticks to confirm accuracy; it was used in Europe before it received FDA approval in September 2017.[2] This system uses a sensor wire that is inserted below the skin surface to constantly monitor glucose levels. Patients who use the product wave a mobile reader over a flat, half-dollar size disc to determine if their blood glucose levels are in, above, or below range, and where their glucose levels have been over the past 8 hours.

Because the product is less expensive than competing glucose monitoring systems, some experts believe it will be the system that will penetrate the T2D market in the United States, where comparatively few of the estimated 29 million who have this type of diabetes use continuous glucose monitoring (CGM) systems.[3] This occurs despite the growing consensus that time in range is a more important measure for long-term health in diabetes care. A consensus statement on time-in-range targets when using CGM was released at the Scientific sessions (see **SP238)**.[4] Indeed, during its April 2019 investor call, Abbott reported a 70% increase in first quarter sales for the FreesStyle Libre over the prior year.[5] Abbott has filed with the FDA for its Libre 2 product under the new interoperable CGM pathway, which requires the system to meet multiple performance standards.[6]

"Doctors tell us that FreeStyle Libre is changing the course of care for people with diabetes, and the combination of these real-world data and clinical research is further proof that our technology delivers significant reductions in [A1C] in people with type 2 diabetes," Mahmood Kazemi, MD, divisional vice president, global medical and scientific affairs for Abbott Diabetes Care, said in a statement released during the Scientific Sessions.[7]

Abbott officials said that the FreeStyle Libre system is now used by 1.5 million individuals in 46 countries.[7] The statement noted that full or partial reimbursement is available in 33 countries, including France, Ireland, Japan, and the United Kingdom. Medicare covers FreeStyle Libre and a few other glucose monitoring systems for those with type 1 diabetes (T1D) and for patients with T2D who can demonstrate intensive insulin use, typically at least 4 injections per day. Historically, Medicaid has had limited coverage for CGM, but this is changing, Abbott officials said in an email to *Evidence-Based Diabetes Management™*.

In the email, Abbott said most US commercial payers cover the system for patients with both T1D and T2D who use intensive insulin. Besides covering CGM through their medical policy under durable medical equipment, the email said, "more and more, commercial payers are now placing CGM on their formularies, allowing patients to obtain CGM at their retail pharmacy." ◆

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Managing Costs in Diabetes Means Intervening Early to Avoid Complications Later, Experts Say

Mary Caffrey

TO SHOW WHY DIABETES HAS become a public health crisis, Peter Butler, MD, the renowned endocrinologist from the University of California at Los Angeles (UCLA), tells the story with pictures: The food portions are bigger. The amount of time spent in front of screens last longer. The distances we commute are farther. Too much eating and sitting do not add up to good health, he explained, creating a $327 billion tab for diabetes just in the United States.[1]

What's worse, Butler said, "We've exported our lifestyle," making diabetes, driven by rising obesity rates, a growing global threat. In 2018, the journal *Diabetes* estimated there are 500 million cases of type 2 diabetes (T2D) worldwide, and rates are comparable between wealthy and poor countries.[2]

"Clearly, we have to take care of people and manage it," he said.

To understand the challenges that health systems face—and what must be done do to meet them—Butler, the division chief of endocrinology and director of the Larry Hillblom Islet Research Center at UCLA, hosted the April 17, 2019, session of the Institute for Value-Based Medicine®, "Diabetes Management: Advances in Treatment and Management to Reduce Cost and Improve Outcomes." The session, presented by *The American Journal of Managed Care*®, explored how investing in better interventions—from newer therapies to improved monitoring to more attention to the whole person—leads to better health and saves money in the long run.

An all-star lineup joined Butler at the Loews Santa Monica Hotel: Anne L. Peters, MD, professor of medicine at the Keck School of Medicine at the University of Southern California (USC) and director of the USC Clinical Diabetes Programs; Karol E. Watson, MD, PhD, FACC, director of the UCLA Barbra Streisand Women's Heart Health Program, codirector of the UCLA Program in Preventive Cardiology, and director of the UCLA Cardiology Fellowship; and Sachin H. Jain, MD, MBA, president and chief executive officer for CareMore Health.

Getting Empagliflozin on Formulary: A Case for Cost-Effectiveness

Peters is not a typical diabetes expert. Besides being involved in cutting-edge research in both drug and device development, she splits her time between patients on both the west side of Los Angeles County, where most patients have health coverage, and the east side, where she said, "there are some of the saddest stories you've ever seen."

Her service on the county's Department of Health Services formulary committee offera a front-row seat for debates about price and value. "One of the things I know the most about is cost," Peters said. She's had to make the case that certain therapies that may have higher acquisition costs ultimately save money by preventing complications that occur when diabetes is not well controlled.

She is not a fan of insulin or sulfonylureas, but she recognizes that both will stay on formulary in T2D for now. But Peters succeeded in getting empagliflozin on the Los Angeles County formulary 2 years before the EMPA-REG OUTCOME trial results were reported.[3] She told the IVBM attendees how she convinced the committee that the sodium glucose cotransporter 2 (SGLT2) inhibitor was keeping patients out of the hospital for heart failure—a result that has been borne out across the class in multiple studies.[4-6]

With empagliflozin, she said, "You get an immediate benefit." For low-income patients especially, that makes a difference. "Heart failure is so hard for these patients. It's heartbreaking. They don't have the home environments where they can deal with sodium and everything else that would really make their lives better."

Overall, avoidable complications persist in diabetes. Peters said only 14.3% of adults with diabetes reach all of their targets—not just glycated hemoglobin (A1C), but also blood pressure (BP) and cholesterol,[7] and there are serious knowledge gaps among primary care physicians. "I've asked some of my best internist friends, 'What do you do after metformin?' And most of them look at me blankly. That is not a good start. We've made the algorithm too complicated."

Diabetes causes suffering, Peters said, such as blindness, kidney failure, amputations, and tooth loss. "There's an increased risk of depression and a whole host of other things," she said. "Diabetes is not your friend, but my feeling is, if you take care of it well, none of this stuff has to happen. It's the taking care of it well that matters, and that means access to healthcare, which I think is the most important part of all of this."

As patients get T2D at younger ages,[8] it's essential to achieve and maintain glycemic control. "A 45-year-old who gets diabetes is someone who is going to live long enough to get complications," she said. This is what costs the health system money. Patients classified as obese, in particular, incur high costs from joint replacements and sleep apnea. "But more than that, their lived experience is miserable."

Even when patients get outstanding care, they remain at high risk for heart attacks. "Every time I hear a patient of mine [died suddenly], I race back to their chart to make sure I didn't miss something," Peters said. "One of the reasons I'm so passionate about this is that most of my patients are really well risk-modified, and they still die.

"I know we're all going to die," Peters said. "But I'd prefer it not be in your 50s and 60s."

> **"There's an increased risk of depression and a whole host of other things. Diabetes is not your friend, but my feeling is, is you take care of it well, none of this stuff has to happen. It's the taking care of it well that matters, and that means access to healthcare, which I think is the most important part of all of this."**
>
> —Anne L. Peters, MD

Which New Therapy Makes Sense in Type 2 Diabetes?

Metformin remains the first therapy patients take when T2D is diagnosed. Now that SGLT2 inhibitors have been shown to have cardiovascular benefits, Peters said, there's an argument to be made that they should be foundational for patients with T2D with comorbid cardiovascular disease. The question becomes: Which of the newer T2D therapies should come next? First Peters, and then Watson, reviewed evidence from a key set of studies—the cardiovascular outcomes trials (CVOTs)—that have fundamentally changed treatment of T2D and brought cardiologists into the mix in the treatment of this condition.

As Watson later explained, in 2008, the FDA began requiring CVOTs to show that new glucose-lowering therapies at least did not cause harm—meaning they did not cause heart attacks, strokes, or other events—to patients with

T2D.[9] Watson shared how the 2015 announcement of the EMPA-REG OUTCOME results[3]—that the SGLT2 inhibitor had reduced hospitalization for heart failure by 35% and all-cause mortality by 32%—hit like a thunderclap. That set off the wave of rethinking among both endocrinologists and cardiologists that culminated with the American College of Cardiologists' (ACC) 2018 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease.[10]

CVOTs for 2 classes of therapy—SGLT2 inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists—have shown results with cardiovascular benefits. Peters reviewed the results and the criteria physicians should consider in deciding which class makes sense for a patient:

Patients at risk of heart failure would likely benefit from an SGLT2 inhibitor.

There are established cut points for estimated glomerular filtration rate to consider when prescribing an SGLT2 inhibitor, and patients with amputation risk should avoid canagliflozin, given the results of CANVAS.[4]

If patients have a compelling need to minimize hypoglycemia and they need to lose weight, a GLP-1 receptor agonist is a good choice.

A1C Is No Longer the Measurement That Matters

Peters concluded with a discussion about moving away from A1C as the holy grail of measuring glycemic control. Use of continuous glucose monitoring (CGM) systems has highlighted the importance of time in range—which tells patients and physicians what percentage of time a person's blood glucose stays out of hypo- or hyperglycemia, or between 70-180 mg/dL. Time in range, she said, is a much better indicator of a person's likelihood of developing microsvascular and macrovascular complications. With the availability of factory-calibrated systems, such as Dexcom's G6 and Abbott's Freestyle Libre, or the Eversense implant that requires no day-to-day involvement from the patient, a more complete picture emerges of the importance of maintaining glycemic control.

"The thing we know from these devices is that probably the A1C is a useless number," Peters said. The next step is moving toward consistency in CGM reports, more like those that come from an electrocardiogram.

Use of CGM allows physicians to demonstrate to insurers that even if a patient's A1C seems normal, if time in range is volatile, a person with diabetes needs the glycemic control that an SGLT2 inhibitor provides to avoid long-term complications. Peters expects that re-examining data from landmark studies like the Diabetes Complications and Control Trial will show the link between time in range and retinopathy or nephropathy. Thus, using CGM "will help us find the patients who need more or less help."

"But it's going to take a lot of teaching to get people to understand CGM," she said.

For Cardiologists, "This Is Your Lane"

For years, Watson explained, the success that cardiologists saw in managing lipids and high blood pressure—due in large part to improved therapies—wasn't repeated when it came to diabetes. "Peter and I and Anne and I have patients in common, who, despite perfect lipids and blood pressure, were still having events, which is heartbreaking," she said.

"We know cardiovascular disease is the leading cause of death and morbidity for patients with diabetes, and it costs a lot of money," Watson said. "And we know that it comes with a lot of co-existing risk factors like hypertension or dyslipidemia, but it doesn't matter…I can get their lipids perfect, I can get their blood pressure perfect, and diabetes itself is going to confer increased risk."

But getting cardiologists involved in diabetes care, to encourage them to target this risk with antihyperglycemic agents, represents a change in thinking. And this was the point of ACC's Expert Consensus Pathway document. "It's one of the most revolutionary documents that ACC has ever released," she said. "We're trying to get cardiologists to understand: This is your lane."

Watson said the document has 3 essential points: (1) Cardiologists should screen for T2D, (2) they should treat the risk factors, and (3) they should treat with antihyperglycemic agents, specifically SGLT2 inhibitors and GLP-1 receptor agonists. "We understood that when we put out this document, cardiologists would need a lot of hand-holding."

The document further identified empagliflozin as the preferred SGLT2 inhibitor, and liraglutide as the preferred GLP-1 receptor agonist; as Peters did, Watson identified SGLT2 inhibitors as the preferred class for those at risk of heart failure. If patients have osteoporosis, are overweight, or are at risk for amputation, GLP-1 receptor agonists may be the better choice.

SGLT2 inhibitors, Watson noted, compare favorably in treating heart failure to many drugs developed specifically to target this condition; several trials are studying this class in heart failure for patients with and without diabetes. The first studies will report findings in 2020.[11-15] "I'm putting my money on the agents," she said.

Evidence Propels Change in Thinking

Prescribing antihyperglycemic agents is just one area where cardiologists have shifted their thinking in light of new evidence, Watson said. Besides ACC's Expert Consensus Pathway, updated primary prevention guidelines[16] reflect recent findings:

Aspirin. Watson said the ASCEND trial results, which showed that taking aspirin for primary prevention reduced vascular events but was offset 1:1 by bleeding risk, was "the nail in the coffin" for giving aspirin to older adults who do not have coronary heart disease.[17] Under the new primary prevention guideline, ACC has sharply curtailed who is recommended to receive daily aspirin.

Hypertension. New guidelines adopted in 2017 by ACC and the American Heart Association redefined what constitutes high BP and lowered the threshold for treatment, based on the SPRINT study results.[18,19] BP ≤120/80 mm Hg or below is considered normal. Systolic BP >120 and ≤130 mm Hg is elevated; stage 1 high BP is defined as systolic BP >130 and ≤139 mm Hg or diastolic BP >80 and ≤89 mm Hg. Stage 2 high BP is defined as systolic BP <140 mm Hg or diastolic BP <90 mm Hg.

Cholesterol. Watson was an author on the 2013 guidelines that identified 4 groups that need statins: (1) patients who have had an event, (2) patients with low-density lipoprotein (LDL) cholesterol above 190 mg/dL, (3) patients with diabetes, and (4) very-high-risk primary prevention patients, based on age and other factors.

The idea of cardiologists screening for diabetes and treating risk factors is new, but necessary, Watson said. "If we don't do something to improve outcomes in patients with diabetes, they're going to keep having events, and that's why cardiologists are going to become diabetologists."

Organizing Healthcare Delivery Around the Whole Patient

So, if every patient just gets the right medication, we can solve this problem called diabetes, right? If only.

CareMore's Jain reminded the providers gathered at the session of a disturbing fact: "We are developing 21st century medicine with a 19th century delivery model," he said.

The idea that closing the gaps in healthcare is as simple as making patients better consumers might make sense to economists and people who don't practice medicine, Jain said. Then he shared an anecdote that illustrated how the solutions being developed for consumers don't always match the needs—or desires—of the people who use the most healthcare.

Early in his career, Jain served in the Office of the National Coordinator (ONC) for Health Information Technology. So, when he was home visiting his family recently, his mother asked him to put that experience to use and set up all her patient portals with her doctors.

The bell went off that so much money and time has been expended on something that has very little value for his mother. "There is the false idea that people want to use this stuff," he said, that patients are going to order healthcare the way they order things on Amazon.

Patients with chronic disease, the kind of patients that CareMore sees, are likely not using

continued

this type of technology in a meaningful way. The health system held a town hall with them at a hotel and listened to what the patients had to say.

"Healthcare should anticipate and deliver on people's needs," he said. Instead of giving them choices they don't understand, healthcare should understand that expertise matters and that the cheapest solution may not be the best one.

The idea that poor people need "skin in the game" to responsibly use healthcare is also out of touch. "People should not pay out of pocket for the things they need," he said. "We should not have co-pays for the things that people need to live," such as insulin.

If health systems want to keep patients from returning to the hospital, then things like using Lyft to get them home, ensuring there's a healthy meal waiting for them when they arrive, making sure they have social contacts, and confirming that they see the same doctor for follow-up care all matter.

CareMore has pioneered services like toenail clippings because they offer regular touch points with the healthcare system, Jain said. When the average daily cost of a hospital bed in Los Angeles County is $3500 to $4000, he said, "You can buy a lot of prevention" by focusing on cost avoidance. CareMore integrates dental coverage and uses a patient's time in the chair to check on other vital signs. Its Togetherness Program touches at-risk seniors who either live alone or need support to adhere to medications or get engaged in community or fitness programs.

How does CareMore do it? The fully integrated care and delivery system for Medicare and Medicaid patients is fully at risk, because as Jain puts it, CareMore's way of doing things would not be possible in "our broken fee-for-service delivery system."

"We believe risk is freedom," he said.

So, when Butler asked how to explain why the field of diabetes has better drugs than ever, but the average A1C is not better than it was 10 years ago, Jain said the need to reinvent the delivery system is the issue.

"A lot of the talk in health policy is around delivery science," he said. "A lot of what we need is more common sense. Radical common sense." ◆

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