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JULY 2017

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AJMC PEER EXCHANGE™ | DIABETES Stakeholders Summit

Understanding Value in Treatment & Technology

AJMC® DIABETES STAKEHOLDERS SUMMIT

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Contents JULY 2017

AJMC® Diabetes Stakeholders Summit

From the Chairman

We present this special issue of *Evidence-Based Diabetes Management*™ (*EBDM*™) featuring coverage from our Diabetes Stakeholders Summit, a series of 3 Peer Exchange™ panels all chaired by Dennis Scanlon, PhD, of Pennsylvania State University and the associate editor of *The American Journal of Managed Care*®. Robert A. Gabbay, MD, PhD, FACP, senior vice president and chief medical officer at Joslin Diabetes Center and editor-in-chief of *EBDM*™, took part in all 3 panels. The first discussion was a timely update on the role of diabetes therapy in preventing cardiovascular events—a follow-up to our 2016 discussion of the groundbreaking results from the EMPA-REG OUTCOME trial. As this year's update showed, we continue to learn more about the possibilities of empagliflozin and sodium glucose co-transporter-2 (SGLT2) inhibitors more broadly. Related coverage in this issue from the 2017 meeting of the American College of Cardiology provides context for the panelists' remarks on where research is headed, as clinicians explore whether SGLT2 inhibitors could offer protective effects against heart failure. Other panel discussions at our April summit asked how clinicians can evaluate the value of recently approved ultra long-acting insulins and combination therapies of insulin and glucagon-like peptide-1 receptor agonists. Finally, our panel discussion on the growing role of technology in diabetes care covered territory from prevention apps to insulin pumps to continuous glucose monitors—while offering a hint of what was to come. Kenneth Snow, MD, MBA, a medical director for Aetna, said we could count on seeing risk-based contracts for diabetes technology soon—and he was right. As this issue went to press, Aetna and Medtronic reached an agreement for Medtronic's pumps, including the new 670G. Our ability to present information that stays one step ahead of the news shows the value of our Peer Exchange™ series, which brings together the stakeholders who are making decisions that affect patient care.

We hope you enjoy the coverage presented here, and visit ajmc.com to view the full programs. ■

Mike Hennessy, Sr
Chairman and CEO

From Unexpected CV Benefits to Potential in Heart Failure: Insights and Outlook for SGLT2 Inhibitors

Mary Caffrey


INZUCCHI


SCANLON

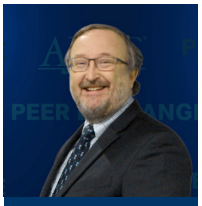
In September 2015, results from the EMPA-REG OUTCOME trial stunned the medical world: for the first time, a treatment for type 2 diabetes (T2D), empagliflozin, was found to have cardiovascular (CV) benefits.[1] The good news about the sodium glucose co-transporter-2 (SGLT2) inhibitor did not end there, however. Researchers have continued to pore over data, finding evidence of additional benefits.

In April, *The American Journal of Managed Care*® convened its second Diabetes Stakeholders Summit. Moderator Dennis P. Scanlon, PhD, professor of health policy and administration and director of the Center for Health Care Policy and Research in the College of Health and Human Development at Pennsylvania State University, University Park, Pennsylvania, led the Peer Exchange™ panel discussion, "Diabetes Therapy and Cardiovascular Outcomes: An Update." Joining him were Silvio Inzucchi, MD, medical director for Yale Diabetes Center, New Haven, Connecticut; Zachary Bloomgarden, MD, clinical professor in the Division of Endocrinology, Diabetes, and Bone Disease of the Department of Medicine at Mount Sinai, New York, New York; Robert A. Gabbay, MD, PhD, FACP, senior vice president and chief medical officer, Joslin Diabetes Center, Boston, Massachusetts; and Kenneth Snow, MD, MBA, medical director, Aetna.

Inzucchi explained that for years, diabetes providers had been frustrated by the fact that correcting a fundamental feature of the disease—hyperglycemia—had little or no effect on CV outcomes. "We can reduce retinopathy, and nephropathy, and probably neuropathy," he said. "But when you look at studies over many decades, it's been very difficult to demonstrate that lowering glucose with a specific strategy or any drug actually benefits the heart." »


BLOOMGARDEN


GABBAY


SNOW

EMPA-REG OUTCOME didn't set out to find a CV benefit. The trial's purpose was to show that empagliflozin was safe, in the wake of events in the mid-2000s that suggested rosiglitazone caused heart attacks. While the FDA ultimately cleared rosiglitazone, the saga paved the way for new protocols that require diabetes and obesity therapies to demonstrate safety for those at high risk of heart attack or stroke.[2]

Inzucchi made an important distinction about what the trial did and did not find. "I think what EMPA-REG OUCOME showed us is that you can improve cardiovascular outcomes, perhaps not through lowering glucose, but through using a glucose-lowering therapy," he said. This was the first time a diabetes drug was shown to have a benefit for CV mortality, and it was associated with a 38% reduction.

"I must say, when I saw these results—and I was on the steering committee for the trial—I almost fell out of my chair," Inzucchi shared with the panel. He was struck that a diabetes therapy that was effective, but not hugely powerful, in lowering blood glucose, could bring such a result in reducing CV death.

It's important, he said, not to overinterpret the results, as EMPA-REG OUTCOME involved patients at high risk or established CV disease (CVD). "Primary prevention, in terms of patients without prior history of CVD, has not been demonstrated," he said.

As much as researchers are still gleaning information from EMPA-REG OUTCOME—and still learning about SGLT2 inhibitors generally—the trial is a breakthrough and has changed the thinking about treating diabetes in many ways, Gabbay said.

Snow agreed. "Certainly, one of the major driving forces for why we treat diabetes to begin with, and why payers pay for the treatment of diabetes is not so much because we want to see lower blood sugar, but because we want folks to live longer, healthier lives," he said. "And ultimately, these types of outcomes trials, particularly if we are seeing reductions in major cardiovascular events, are exciting."

What Do We Know About SGLT2 Inhibitors?

The SGLT2 inhibitor drug class has a completely different mechanism from other antidiabetic therapies. The drugs target a protein that normally reabsorbs glucose in the kidney, and instead blocks this function and causes excess glucose to be expelled in the urine. Scanlon asked Gabbay what researchers have learned about the mechanism of action of SGLT2 inhibitors that explains the results found in EMPA-REG OUTCOME.

"It's a great question," Gabbay said, adding that the results surprised many. There's been a lot of "thinking backward," to truly understand how SGLT2 inhibitors work, and therefore, how they achieve what they do. "What we do know about SGLT2 inhibitors is that they result in a little bit of diuresis and volume contraction, and that, certainly, could be one of the factors [particularly in terms of congestive heart failure incidences and hospitalizations for congestive heart failure], for which they saw a benefit. There's also a small amount of weight loss, which could also be a factor."

As he explained, regression models using data from the EMPA-REG OUTCOME trial estimated that about half the effects could be related to volume. Another correlation that merits further study involves uric acid levels.

"There's another finding of the empagliflozin trial, which is fascinating and may shed light on this—the effect on renal disease," said Bloomgarden. EMPA-REG OUTCOME showed that empagliflozin was not simply a diuretic, but also acted on sodium secretion; it worked in the kidney "in a lovely way with angiotensin blocking agents," Bloomgarden said.

"So, at the level of the macula densa, delivering more sodium to that part of the kidney seems to then potentiate the benefit of not having so much angiotensin action on board," he said. "Well, this fits very nicely into a lot of our clinical knowledge of what's good for heart failure and our theoretical ideas of what's good for the heart and what's good for the kidneys."

A New Indication for Empagliflozin

Scanlon asked the panel to discuss an FDA decision to add a new indication to empagliflozin, to reduce CV death in patients with T2D.[3] What, he asked, are the clinical decision-making implications?

Payers face challenges, Snow said, in deciding whether the effect is just for empagliflozin or a class effect that applies to other SGLT2 inhibitors. "Is it in all patients or only those with preexisting heart disease?" Snow asked. "These are research questions that are still in the process of being answered, and somehow, in the process, there needs to be a decision on coverage."

Bloomgarden said that if other trials do not show benefits, it would be difficult for any payer to not

provide empagliflozin to patients with known heart disease, "of which there are so many."

"At the very least, there are now data out there about the population of folks who clearly got a benefit with a particular agent," Snow said. "And now, really the question is, is it unique and is it unique to that population?"

CV Benefits in the GLP-1 Class

Scanlon asked Bloomgarden to comment on the LEADER trial, which found that liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, also had cardioprotective benefit: results presented at the 76th Scientifiic Sessions of the American Diabetes Association (ADA) in June 2016 showed it reduced CV death in high-risk patients by 22%.[4] Results presented at ADA the year prior for another GLP-1, lixisenatide, had shown only that the drug was safe, not that it had demonstrated any CV benefit.[5]

"LEADER was fascinating, coming as it did, immediately after the EMPA-REG OUTCOME trial," Bloomgarden said. "The strategy was a little bit different. The centers were asked to try to achieve good glycemic control in the patients in the control group and the patients in the liraglutide group, so that there was an up-titration of nonliraglutide, non-GLP-1 receptor agonist therapies in the control group." From his vantage point, liraglutide's benefit was that it allowed clinicians to avoid the harms of older medications like sulfonylureas.

Inzucchi agreed. He discussed results for SUSTAIN-6, which found a CV benefit for semaglutide, a once-weekly GLP-1 that is not yet available.[6] "It seemed that the most potent effect was actually on stroke, which was surprising because that's not what you see with atherosclerosis trials," Inzucchi said. "You typically see it on nonfatal (myocardial infarction) and, maybe, cardiovascular mortality."

For Inzucchi, the differences point up the importance of not assuming anything. "It leads us to understand that you cannot appreciate the effects of these individual drug categories until you get at least 3 or 4 trials under your belt so you can see the overall effect of the class," he said.

SGLT2 Inhibitors and Heart Failure

Recently, increased attention has been given to the idea that SGLT2 inhibitors could have a role in primary prevention of heart failure (HF) for the broader population with diabetes, not just patients at high risk for CV events. The presentation of results for the CVD-REAL trial in March 2017 at the American College of Cardiology[7] (which were followed by a paper presented in June at the 77th Scientific Sessions of the ADA[8]), involved the use of more than 300,000 patient records from 6 countries to study the effect of SGLT2 inhibitors. Researchers found a 39% reduction in rate of hospitalization for HF and a 51% reduction in death for any cause.[7]

Bloomgarden explained the relationship between diabetes and HF. "Diabetes is associated with increased likelihood of atherscrotic cardiovascular disease," he said. "And certainly, individuals who have myocardial damage have decreased heart function and are at risk of heart failure."

What is less appreciated, he explained, is how diabetes leads to fibrosis and decreased heart function, and endocrinologists are aware of 2 types of HF in these patients: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). "These are extremely important causes of morbidity and mortality," Bloomgarden said. "People with heart failure feel tired. They have less energy, and then, eventually they progress to peripheral edema, dyspnea, and all the classic things we learned.

When more and more patients with diabetes come in with these symptoms, he said, "it becomes very attractive to say, we may have a specific drug that could be useful."

Inzucchi noted that a secondary endpoint in EMPA-REG OUTCOME showed a 35% risk reduction for hospitalization for HF among patients with T2D with known coronary artery disease.[1] The number of people with high-risk T2D and existing heart disease is "a real epidemic," Inzucchi said. "I think our cardiology colleagues are getting so good at saving people during their acute coronary syndromes that many patients are now living with somewhat damaged ventricles. So, the 35% risk reduction, we saw that and we wondered whether this was something that occurred in patients with established heart failure or whether it was preventing heart failure episodes. And I think the answer is both."

As a result, the EMPEROR studies are now under way for empagliflozin, which will examine the effect of the SGLT2 inhibitor specifically on patients with HFpEF and HFrEF.[9,10] Results will come in 3 to 4 years. "These are heart failure trials being driven by heart failure experts," Inzucchi said. "The heart failure community is very interested in this class because of the EMPA-REG signal, »

ABOUT THE PANEL

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Kenneth Snow, MD, MBA, medical director, Aetna

EMPA-REG OUTCOME: HIGHLIGHTS

Total patients: 7020
(4687 empagliflozin vs 2333 placebo)
Mean observation Time: 3.1 years

No significant differences in rates of myocardial infarcation or stroke, but

- **38% RR reduction in death from CV causes for empagliflozin**
- **35% RR reduction in hospitalization for heart failure**
- **32% RR reduction in death from any cause**

RR indicates relative risk.
Source: Zinman, Wanner, Lachin, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015; 373(22):2117-2128. DOI: 10.1056/NEJMoa1504720.

but the question is, will the benefits be seen again in the diabetic population?"

"Or in prediabetes?" Bloomgarden asked.

Big Data and CVD Benefits

Of course, clues to what the EMPEROR results may reveal were contained in CVD-REAL. Scanlon asked Gabbay to discuss these findings, as well as the importance of using data to gain these insights.

"It's the beginning of what we'll see a lot more of—using big data to try to answer some of these questions," Gabbay said. "There are a lot of hypotheses. Is it a class effect? What's the effect on congestive heart failure? We have some data, but not all the questions are answered. There are a number of studies that are ongoing. Some, we'll get results soon, but some will still take several years. What do we do in the meantime?"

Gabbay explained that while CVD-REAL seemed to suggest a signal for reducing congestive heart failure across all SGLT2 inhibitors, the "challenge with a retrospective analysis is you're not randomizing people to therapy." Gabbay and Inzucchi agreed there was some value in observational studies—as statisticians can use propensity matching to make up for the loss of randomization—but Inzucchi said these studies should be taken "with a grain of salt."

Bloomgarden, too, noted the need to watch for "channeling bias," in observational studies—when patients ask to be put on the "new drug." But he said that even the largest clinical trials have event rates that are so low there are questions that can't be answered. Inzucchi said the question is whether patients in trials are different from those in the real world. "I think it's great when the randomized clinical trials and the observational data sets point in the same direction, but when they don't, I think it's really confusing."

Designing Better CV Outcomes Trials

CV outcomes trials started with one idea, "First, do no harm." But, Scanlon asked, is it time for a redesign? Are they powered sufficiently? As large as they are, are they large enough? How long should patients be followed? Can data be collected retrospectively, and if so, for how long?

Bloomgarden said as "hugely expensive" as it would be to follow large numbers of patients for a decade or more, this must be balanced against the 650 million individuals worldwide who will develop diabetes by 2040. And trials shouldn't just examine the effect of therapies or strategies on the highest-risk patients. "Let's try to figure out how all people developing diabetes should be treated going forward," he said.

Long term, the progression of diabetes makes it impractical to study a single therapy for an extended period, Inzucchi said. "It's not clean like that," he said, using an example of a study conducted in 2004 based on the approaches that were common at the time that resulted in "cross contamination" as patients needed additional therapies.

Snow, the payer, said there's no chance that an analysis of big data will ever replace the role of the randomized clinical trial, "no matter how good it is." However, he said, "we do know that there are certain situations where a randomized clinical trial just doesn't work because the population is relatively homogenous. So, you're stuck with the question of, 'Well, can't I expand this into other populations? Do I need a full, other randomized controlled trial to answer that question or not?' "

Observational studies can help with questions that would take a long time to answer, that would require studies of great complexity, or in cases in which there is great risk of patients dropping out of the study, Snow said.

"I totally agree," Gabbay said. There are many questions that need answers, and not every question will get a randomized controlled trial that collects data for 5 to 10 years. Practically speaking, there are patients who need treatment today.

"As big data [analysis] becomes more sophisticated,...and studies are done more accurately, we're going to have to rely on that kind of data to answer some of the questions that there are unlikely to be clinical trials on," Gabbay said. The challenge is that some will be well done and others will be poorly done, and the average provider reading an abstract won't know the difference. The danger is that kind of data sways clinical care. I think a better arbitration of study technique for big data analysis will really help move the field forward."

Clinical Decision Making and Cost–Effectiveness

Scanlon turned the discussion toward the future—of using data beyond 1 institution or health plan to mine data sets for insights from larger populations, so that clinicians gain a more balanced view than might otherwise happen if they are influenced by an outlier case. Snow said this requires cooperation between plans and providers.

"One of the hopes for the future is that we'll be able to integrate that type of data, more effectively, into the data that we have through various relationships we have with the providers," Snow said, "where we're able to share that information and able to bring the power of the information that's collected on the individual patient level—lab data, physical findings, etc—but also bring it to a level where we're talking about not necessarily hundreds or thousands, but now, talking millions of folks that we're looking at into the analysis."

> **"I must say, when I saw these results—and I was on the steering committee for the trial—I almost fell out of my chair."**
>
> *—Silvio Inzucchi, MD, Yale Diabetes Center on his reaction to the EMPA-REG OUTCOME results*

Coverage decisions, he said, start with the scientific evidence. "That's separate, or divorced, from the cost (either the cost of the therapy or even the savings). Once the scientific data are established, that it's effective, then the question (that) comes is, 'What is that cost? And how is it going to fit into a benefits plan?' "

"And so, obviously, it's about something that, in addition to being scientifically valid, also saves money. Well, that's about as easy as it gets.

"Those that are scientifically valid and cost some money; those are very likely to still be approved. And those that are scientifically valid but cost a lot of money may still well be approved, but they may get more scrutiny to make sure they're being utilized for the appropriate patient in the appropriate way."

Snow acknowledged that the time element does enter the cost-effectiveness discussion—will the payer of today realize the benefit for an expensive therapy that may prevent costly events years into the future?

Gabbay said that is where "class effect" become important. Once a class of drugs is shown to have a benefit, payers may choose among different drugs based on price. "But if it turns out that there's ambiguity there, and right now, we're still in an area of some ambiguity, it makes that much more problematic.

"That's really where I think we'll have a sense, over the coming months, of whether studies now confirm that there's a class effect or not. For most other drugs, that has been the case."

The panelists concluded by discussing how this is an exciting time in diabetes care.

"Diabetes has always been one of those situations in medicine where there was just a very negative association with it," Snow said. "It's increasing in frequency. The prevalence of diabetes is increasing. Folks will develop microvascular complications…the news is always bad."

But now, "We have slowly chipped away at the microvascular complications and we've chipped away at the macrovascular complications, and now we have even further agents that look like we'll be able to chip away at this big chip much more. And so, we can really give our patients an upscale message that, yes, it's diabetes, but you can live a long and healthy life despite having diabetes." ■

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Finding Value in Today's New Insulins, GLP-1 Combinations

Mary Caffrey


SCANLON


BLOOMGARDEN

Nearly 100 years ago, the discovery of insulin forever changed the lives of people with diabetes. Today, insulin continues to extend lives and improve health for those with both type 1 (T1D) or type 2 diabetes (T2D), as drug companies create improved versions of this metabolism-regulating hormone.

The insulin available today lasts longer and gives patients more dosing flexibility, but it must be balanced with therapy prices and changes in benefit design, which may require higher out-of-pocket (OOP) costs. In April, *The American Journal of Managed Care*® convened its second Diabetes Stakeholders Summit to discuss how to evaluate value in modern insulins and therapies that combine insulin with a glucagon-like peptide-1 (GLP-1) receptor agonist.

Moderator Dennis P. Scanlon, PhD, professor of health policy and administration and director of the Center for Health Care Policy and Research in the College of Health and Human Development at Pennsylvania State University, in University Park, Pennsylvania, led the Peer Exchange™ panel discussion "Finding Value in Today's Insulin Therapies." Joining him were Zachary Bloomgarden, MD, clinical professor in the Division of Endocrinology, Diabetes, and Bone Disease of the Department of Medicine at Mount Sinai Health System, New York, New York; Robert A. Gabbay, MD, PhD, FACP, senior vice president and chief medical officer, Joslin Diabetes Center, Boston, Massachusetts; Mary Ann Hodorowicz, RDN, MBA, CDE, CEC, a Chicago, Illinois–based consultant, dietitian, and trainer; and Kenneth Snow, MD, MBA, medical director, Aetna.

Scanlon called on the panel to describe the changes in the treatment landscape in recent years. Bloomgarden noted there certainly are more choices—up from a pair of medication classes to more than 10—allowing clinicians to individualize therapy (including GLP-1s and sodium glucose co-transporter-2 [SGLT2] inhibitors). While metformin is still considered the starting point,

Bloomgarden said, "many people do have advanced renal disease and should not be treated with metformin."

Gabbay outlined a host of considerations: potential for weight gain, adverse effect profile, costs, patient coverage, and the suitability of injections for a particular patient. Hodorowicz pointed to the need for considering the challenges of diabetes: Is the patient struggling with preprandial blood glucose, postprandial blood glucose, or both?

"We are aiming for excellent glycemic control in as many of our patients as possible, recognizing that we want to avoid hypoglycemia, weight gain, gastrointestinal side effects—all of these issues that plague us," Bloomgarden said. "And we want to avoid undue expense while recognizing that some of the less expensive medicines with more side effects may ultimately be less desirable."

The panelists noted disagreement among professional societies on when to start patients on insulin, which Gabbay said creates challenges for the primary care physician. In general, providers probably wait too long, Snow said. "Part of that clearly reflects the patients' concern about starting insulin, but part of it reflects the providers' concerns—or at least some providers' concerns—with using insulin in their patients," he said.

Gabbay reiterated the need for individualization: "Unfortunately, there haven't been a lot of randomized trials to be able to say, 'Second-line drug—what's the best choice?' It really ends up being based on logic." For example, if a patient is at high risk of cardiovascular disease and a drug has been shown to lower that risk, that "makes that choice better," he said.

Once it's clear a patient needs therapy beyond metformin, it's "extraordinarily complex with a lot of nuance," Snow said. "What we prefer to look for [as payers] is whether it makes reasonable sense and whether folks are achieving good control." There may be disagreement between a target of 7% or 8% for glycated hemoglobin (A1C),[1,2] "but everyone agrees it should never be 9%," he said.

Today's Insulins versus Older Formulations

Prescribing habits for patients with T2D changed with the introduction of U100 insulin glargine (Lantus), because most patients could achieve good glycemic control with 1 dose a day, Bloomgarden said. He described the "unique advantages" of recently introduced ultra–long-acting insulins (U300 insulin glargine, sold as Toujeo, and insulin degludec, sold as Tresiba). "With both of these products, there may be a little bit less variability of action. These may [provide] a little bit of a smoother insulin curve," he said. "These are these treat-to-target studies against U100 insulin glargine. And in both cases with both insulins, and in people with type 1 diabetes and type 2 diabetes on basal insulin alone and type 2 diabetes on basal bolus—basically every situation where a treat-to-target trial has been done—they've shown less nocturnal hypoglycemia, which is certainly good. Insulin degludec has the additional advantage that it really can be given at a different time of day on different days," Bloomgarden continued. "So, if the person takes it one day in the morning, and then the next day forgets to take it in the morning but takes it in the afternoon, it actually works fine. And the flatness of it is such that you get fairly stable blood insulin levels without causing hypoglycemia"—helpful with older patients for whom family members are caregivers. This flexibility could lead to better adherence, Gabbay added.

When it comes to coverage decisions, Snow said, ideally, there should be no dramatic difference in cost. "What you hope for is that as there are additional insulin options available...[so] that the price doesn't become the driving force, but, rather, that the appropriateness for a particular patient becomes the driving force," he said.

Bloomgarden agreed: "I would just absolutely echo that."

Health plans, providers, and patients must balance the advantages with the costs of the newer insulins. Gabbay recently wrote an editorial in *Evidence-Based Diabetes Management*™ that discussed the complexity of the debate over prices.[3] "There isn't 1 bad guy or 1 bad player in all of this—it's sort of a series of difference pieces," he said.

Greater transparency would help, Gabbay said, and Hodorowicz agreed that it's difficult when an endocrinologist takes time to match an insulin with a patient's needs, only to learn that the drug is not covered.

Because of changing benefit designs, OOP costs are an issue and can affect patient behavior. "I have, unfortunately, seen people who simply say, 'I won't use more than 1 syringe worth of insulin.' It really is a dilemma," Bloomgarden said. When Medicare patients reach the point in the year when they have a coverage gap, cost sharing temporarily becomes a big problem »

ABOUT THE PANEL

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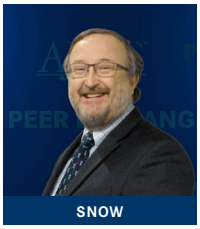
SNOW


HODOROWICZ

until they move through the "donut hole." (Starting in 2017, changes to the law will allow Medicare patients to close the gap more quickly.[4])

The DEVOTE Study, Formulary Decisions, and Busy Clinicians

The Peer Exchange™ took place shortly before Novo Nordisk submitted data to the FDA asking that the label of insulin degludec be updated to reflect data from the DEVOTE trial, a head-to-head cardiovascular (CV) outcomes trial that found that 27% of patients experience severe hypoglycemia compared with those taking insulin glargine.[5] Full results from DEVOTE, presented in June at the American Diabetes Association 77th Scientific Sessions, showed that insulin degludec offers the same level of CV safety as insulin glargine, as well as a 40% overall reduction in hypoglycemia.[6]

From these data, which involve patients at high risk of CV events, payers look at the evidence to make formulary decisions. Snow outlined the steps involved.

1. Examine the evidence for what offers a benefit versus what is questionable.
2. Negotiate to give patients options to improve cost.
3. Hold costs down while keeping an array of options for a particular member.
4. Make exceptions for members who are allergic or have a failure on a therapy.

The process is very fluid. Even within a plan, there are different levels of pharmacy benefits, Snow said. "You could have 5 patients in a row with the same insurance, and yet they have 5 different drug plans," he said. "It's something that computers should be aiding the busy clinician with."

Advance knowledge about a patient's coverage options would help, Bloomgarden said. Gabbay agreed. "It's a solvable problem, and it's mind-boggling that it hasn't happened," he said.

A Marriage Made in Heaven

Scanlon introduced a discussion of combination therapies: insulin with GLP-1 receptor agonists, which have been approved for patients with T2D. The FDA approved both drugs on the same day: Xultophy, which combines insulin degludec and liraglutide (from Novo Nordisk), and Soliqua, which combines insulin glargine and lixisenatide (from Sanofi).[7]

"It's like a marriage made in heaven," said Hodorowicz. "The GLP-1 [agonists] have 3 main mechanisms of action: they increase glucose-dependent insulin secretion, which is wonderful; decrease glucagon secretion (so the liver is not generating glucose); and decrease gastric emptying (for better postprandial, postmeal blood sugar control). So, you combine those 3 mechanisms of action from the GLP-1 [agonist] with the insulin's ability to lower pre- and postprandial blood glucose. It's like a 4-way marriage made in heaven—these 3 functions of GLP and then the insulin."

Bloomgarden explained it another way: "We have known for a long time that after basal insulin, you often go to basal bolus, where you give insulin before meals... but there's an entirely different way of achieving this, which is basal insulin plus a GLP-1 receptor activa-

tor. And that essentially gives you a better version of basal bolus insulin."

Patients can delay gastric emptying and achieve good glycemic control, with less weight gain and less hypoglycemia, Bloomgarden said. The combination allows the patient to take less of the GLP-1 therapy, which can reduce the gastrointestinal adverse effects, the Achilles' heel of this class.

Payers must consider a balance when offering the 2 therapies in a single injection, Snow said. "The opportunity to combine them into 1 syringe—of course it's better for the patient. It's easier—it's only 1 injection versus 2," he said. In similar situations, this has improved adherence. "It's not medically going to be any better, so in a way it's a convenience issue—but a very important convenience issue if they're not adherent [with separate injections]."

All stakeholders—managed care, pharmaceutical companies, physicians, and patients—must be on the same page, Bloomgarden said. "If it exists as 1 shot, and it's so much easier for the human being with diabetes to accept 1 injection than 2, let's all strive to make that 1 injection available because it will pay off," he said.

"Framing in terms of adherence, as you did, I think really is *the* issue," Gabbay said. "Medicine only works if people are adherent to it."

> **"Every one of us who tries to treat people with diabetes feels that this is a human being who's struggling with this disease. We really can help people by using these newer treatments. And, of course, the managed care companies have helped us to make it available."**
>
> *–Zachary Bloomgarden, MD, Mount Sinai Health System*

Selecting the Right Therapy

"So, with all these medication improvements, what are the key challenges?" Scanlon asked.

Hodorowicz framed her answer in terms of the AADE7: 7 evidence-based behaviors identified by the American Association of Diabetes Educators, which include medication. A challenge with newer therapies is that patients are not referred for education on proper use, and physicians often do not have time to teach them in a 10- to 15-minute appointment. "It's not a good situation," she said.

Gabbay agreed that diabetes educators are underutilized. "I think it's a big issue, and it's more than just reimbursement, because even in places where there is reimbursement, they're still underutilized," he said. "Providers may not realize the benefit, and also, I think patients probably don't like the term 'education.' "

Each panelist offered final thoughts, starting with Bloomgarden. "Every one of us who tries to treat people with diabetes feels that this is a human being who's struggling with this disease," he said. "We really can help people by using these newer treatments. And, of course, the managed care companies have helped us to make it available. Even though we grumble a lot, without the insurance companies supporting the patients' use of this, we could never do it. So it's a challenge."

"We can individualize care much more effectively based on what the needs of the patient are," Gabbay said. "We talked about a number of factors to consider: hypoglycemia, weight gain, and other comorbidities." In terms of cost, transparency would be an important first step. "That said, I think there's so much improvement that can be made in diabetes care, and we have so many more tools to be able to do it now than ever," he said.

"Insulin has to be—in all its forms, in all its devices to inject it—for the patient, affordable; accessible per the payer and the mail order pharmacies; and appropriate—individualized for patients' unique lifestyle needs, metabolic needs, [and] complication needs," Hodorowicz said.

"We need to be sure that it's being utilized as frequently as it needs to be," Snow said. "For type 1, that's easy, in a way, because it's absolutely essential for life. But, for so many folks with type 2 who clearly have a need to move beyond the therapy they're on to achieve the level of control that they should, insulin is still almost 100 years later a wonderful drug—and needs to be available for those folks, so they can achieve that control and stay healthy." ■

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With Rise of Diabetes Technology Comes Value-Based Payment

Mary Caffrey


SCANLON


GABBAY

With seemingly everyone having a smartphone and carrying it everywhere, it was only a matter of time before apps took center stage in efforts to prevent and manage diabetes.

But figuring out how to connect health plans with this technology is proving complicated. Medicare's efforts to launch the Diabetes Prevention Program (DPP) by early 2018 have slowed as it works to include digital providers, which are needed to scale DPP to all who will need the program.[1]

Even paying for more conventional devices isn't always straightforward. As diabetes technology evolves, patients want more choices, whereas payers want to hold down costs.

To delve into these issues, *The American Journal of Managed Care*® (*AJMC*®) hosted the discussion "Technology in Diabetes Care: From Prevention to Disease Management" during its April Diabetes Stakeholders Summit, a Peer Exchange™.

Moderator Dennis P. Scanlon, PhD, professor of health policy and administration and director for the Center for Health Care Policy and Research in the College of Health and Human Development at Pennsylvania State University, in University Park, Pennsylvania, led the discussion. Joining him were Robert A. Gabbay, MD, PhD, FACP, senior vice president and chief medical officer, Joslin Diabetes Center, Boston, Massachusetts; Mary Ann Hodorowicz, RDN, MBA, CDE, CEC, a Chicago, Illinois–based consultant, dietitian, and trainer; Kenneth Snow, MD, MBA, medical director, Aetna; and Neal Kaufman, MD, MPH, founder and CMO of Canary Health.

The April discussion foreshadowed an important development when Snow said that "without a doubt" the diabetes device world would be moving toward value-based payment models. On June 26, 2017, as this special issue of *Evidence-Based*

Diabetes Management™ went to press, Aetna and Medtronic announced a risk-sharing agreement for patients transitioning from multiple daily insulin injections to Medtronic's insulin pumps, including the new Medtronic MiniMed 670G. The agreement covers patients with types 1 and type 2 diabetes (T1D and T2D). Medtronic's reimbursement will be partly based on outcomes-based measures for patient experience, clinical outcomes, and total cost of care.[2]

Technology and the Diabetes Prevention Program

As the discussion began, Gabbay explained that results from a landmark National Institutes of Health study show that a lifestyle intervention under "very controlled, rigorous conditions" could produce better results than medication (metformin) for preventing diabetes.[3] "The challenge of that study [is that] it was done in a very resource-intensive way to ensure that people adhered to their lifestyle," Gabbay said. "Now, how do you apply that to the broader population?"

That was the early concern for payers, Snow said, even though they were excited about the DPP. Kaufman, who was very involved in the early years of the DPP, weighed in, pointing out that a single trainer could help 30 to 40 people a year because the program required 16 weekly sessions at the start, followed by monthly in-person sessions. Training was done one-on-one.

"The CDC recognized that that was not a scalable or sustainable model and began looking at how to provide it in other ways," Kaufman said, and then described 2 "threads" of approaches. The first, most common approach involves training to 10 to 15 people at once, with highly trained educators leading the groups. The best example is the YMCA pilot study funded by the Center for Medicare & Medicaid Innovation (CMMI), which provided the evidence to scale the program across Medicare.[4]

The second approach is to use technology. The question here, Kaufman said, is whether a program offered in person would translate in a digital format, using a cell phone. "I was very much involved back in 2006 to create a digital version of that program," he said. "At that time, we didn't know if it was going to work. We didn't know if people would accept it, but we recognized that people need choice …

"And so, we, and now a number of other companies, have been able to demonstrate that you can take an in-person program, use great design and great approaches to make technology work, and have individuals use it effectively."

Scanlon asked the panelists to elaborate more on the YMCA study, because it formed the basis for Medicare's decision to fund DPP, a decision that will bring diabetes prevention to seniors on a widespread basis in 2018. Many DPP providers believe that once commercial payers that administer Medicare Advantage see the value of the program, DPP will become even more embedded in health plans.[5] Hodorowicz said that the dynamic of self-monitoring–tracking weight and exercise and keeping a food diary–and having to report to a lifestyle coach increases motivation more than taking these steps alone does.

Scanlon asked if the number of sessions patients must attend helps, as well. Kaufman replied that based on the YMCA study results, it does. The study contributed to the regulations CDC uses for program recognition: 16 weekly sessions, followed by less frequent attendance for a total of 26 sessions.

What about evidence? "This was a big decision for CMS to decide they were going to go ahead and pay for this," Scanlon said, adding that it has not been without controversy. "Will other payers follow?"

Snow noted the enormous impact: "Any decision by CMS, whatever cost there is has to be multiplied by millions." But one difference with Medicare, he said, is that beneficiaries don't leave, so Medicare reaps the rewards of its investment. For other payers, a preventive service may or may not pay dividends if enrollees switch insurers. Still, "some payers have already made decisions regarding continuing coverage similar to CMS," and Aetna is among them, he said. "Some will be looking at the type of data that comes out in the real world and real-life experience to see if the results that are hoped for are actually achieved."

Thanks to the YMCA pilot, Gabbay said, it's no longer theoretical that the DPP saves money. "That, in essence, was exactly what CMMI was set up to do–to be able to do pilot studies that show cost savings or high value, and then spread that more broadly," he said.

When asked by Scanlon to address the role of diabetes educators in offering the DPP, Hodorowicz said that for years, patients with prediabetes were referred to educators but did not quality for coverage, even though a certified diabetes educator was perhaps the best person to help that patient avoid progressing to diabetes. But now, with some commercial payers offering coverage and »

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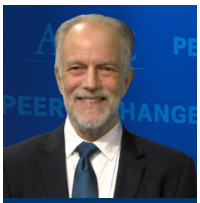
SNOW


HODOROWICZ


KAUFMAN

CMS poised to do so, the American Association of Diabetes Educators is training DPP coaches. "It's an easy fit to include prevention with an existing self-management program run by diabetes educators," Hodorowicz said. "It's a perfect marriage."

Kaufman agreed. If a person is at risk for diabetes, he said, "we need to help them improve their life's trajectory, to help them so that they don't add a new chronic condition every 3 to 5 years, as many people do." That starts with lifestyle intervention. Focusing on the glucocentric requirements of eligibility for the DPP that will help people lose weight and become active is too restrictive, he said.

Once payers have the data, Snow said, they will look beyond the issue of diabetes: Does helping at-risk patients lose weight also help avoid issues such as joint damage or back problems? "[These] are clearly not glucocentric but still related to the same population," he said.

"The real secret sauce is, how do you get people to sign up and show up?" Kaufman asked. "Once you can get them to the program, we can almost predict for 1000 people or 10,000 people what's going to happen. But how do you get the right person to the right program at the right time to engage them, to activate them, to get them to see that there is a benefit?"

Gabbay agreed that for some patients, in-person programs such as the YMCA will be best, but for others, digital solutions will work well. Hodorowicz said she believes that for the younger generation, digital solutions will be more popular, and Snow noted that Medicare enrollees are more accepting of technology than people realize.

It's important to distinguish between a digital tool, such as a text, which acts as a reminder, Kaufman said, and an intervention, which is a full program of health improvement. Gabbay said he regularly uses the smartphone, such as to show patients that they are walking less than they think. By contrast, he said, "if you want to do something to prevent diabetes, you need a whole intervention, based not only on counting steps but also [on] dietary changes and other behavior change approaches."

The Clinical Rationale for Continuous Glucose Monitoring

Scanlon moved the discussion to the importance of continuous glucose monitoring (CGM), now considered the standard of care for those with T1D and becoming more common for those with advanced T2D. A 2011 study[6] in *AJMC*® was the first to quantify the cost of a hypoglycemic admission to the hospital and was cited by JDRF and others in their successful effort to convince the FDA and Medicare to change policies that will ultimately allow beneficiaries to have coverage for the Dexcom G5, although there have been some implementation issues.[7,8]

There's evidence that—particularly for patients with T1D willing to use CGM technology—it shows a benefit, Snow said, both in terms of improving glycemic control and lowering hypoglycemia risk. "Once you get outside of that, causation data becomes very thin," he said, "so you see observational data, where there's clearly a relationship between hypoglycemia and...if you can give them the message that prevents the hypoglycemia event, well, then that is optimal."

The challenge is to make sure that patients have access to both the CGM and the right education, which Hodorowicz said is key, because when patients know how to use the data the device provides, educators can more easily instruct them on how to "embed lifestyle changes." "The good news is that Medicare is starting to cover [CGM]," despite strict criteria, she said.

> **"The real secret sauce is, how do you get people to sign up and show up? Once you can get them to the program, we can almost predict for 1000 people or 10,000 people what's going to happen. But how do you get the right person to the right program at the right time to engage them, to activate them, to get them to see that there is a benefit?"**
>
> *—Neal Kaufman, MD, MPH*
> *founder and chief medical officer, Canary Health*

"It's fantastic news," Gabbay agreed. "At Joslin, we have a large type 1 population, and for them, they reach Medicare age and they have to go off their continuous glucose monitor, which is a big problem," he said. "But I think you'll see, in the not-too-distant future, this spreading to more use in the type 2 [population] based on the kind of evidence that people who are on multidose insulin can clearly benefit."

From a payer perspective, Snow said, the fact that the FDA approved the Dexcom G5 for dosing was reassuring—this was a key step in Medicare's reversal of its longstanding refusal to pay for CGM. "Once you have that FDA stamp of approval, there's significant advantage, not the least of which is it usually means that there's legitimate scientific evidence," he said. "And that scientific evidence is what supports the use."

CGM data will be more reliable than patient logs, which could be helpful with older patients. "That helps diabetes educators and physicians with medication adjustments and lifestyle changes," Hodorowicz said. "With the pediatric population, it's wonderful because parents are so involved with their children's control, especially of type 1."

Audible alerts can help patients or caregivers avert an approaching hypoglycemic event. "Payers are starting to recognize that," Hodorowicz said, "and it's not just for the type 1s, it's also for the type 2s on multiple daily insulin doses."

Devices help, but it's essential that patients already be engaged in their own care, Kaufman said. He pointed to a program developed by Stanford University, the Chronic Disease Management Program, which is decades old and has been highly successful with patients with T2D.[9] "If your A1C was above 9%, it went down by 0.93% at 6 months, and 1.27% at 12 months with a 6-week intervention," he said. "How does it work a year later? Because people change their lives, change their emotions; they change their sense of well-being, and, therefore, they were able to follow doctor's orders better, follow nurse's orders better."

"And that becomes crucial in anything that has to do with self-management," Kaufman added. Scanlon noted that this was work pioneered by Katie Lorig, DrPH, and remains foundational in chronic disease management.

Scanlon and Kaufman discussed the need for peer-to-peer support, either in person or in digital formats. Gabbay noted that vast potential for the latter is "just beginning to be tapped." "Continuous glucose monitoring certainly helps, and even the simple ability of downloading blood glucose meter data and looking at that with the patient is really helpful," he said. Providers don't want too much data, however, and decision support tools help manage it all, which he called the next revolution.

"The next revolution after that," Kaufman said, "is being able to assess it in the moment and give feedback to the individual in the moment." The challenge, he noted, is that managing diabetes requires patients to constantly make micro decisions. No single decision is hugely important; it's the sum of them that determines the outcome. The perfect device would require no interaction.

It's hard to balance the desire for tools without overloading patients to the point of "alarm fatigue," when they tune out the efforts to help them, Snow said, "because it just gets in the way of living."

Payer Coverage, Patient Choice in Insulin Pumps

In this rapidly evolving area, Gabbay said, the FDA appears to be open to approving devices more quickly that it had been. "The floodgates are about to open because there are a whole series of iterative changes that can be made to push forward semiautomated insulin delivery," he said.

As Scanlon noted, however, the issue is figuring out for whom is the device appropriate. "And how do we determine appropriateness?" he asked.

"That's one of the great challenges, because there's not a lot of good data that identifies who makes a good pump user," Snow said. "We can extrapolate [whom] we believe that might be, but there's not really a lot of data that [are] going to predict for the person sitting in front of you, whether they are likely to succeed or fail." »

Gabbay said that this is changing with the movement toward semiautomatic delivery; the bar is no longer as high for patients' carb-counting and insulin-adjustment skills. "You could take patients with poor glycemic control and maybe not terribly adherent and [put them] on semiautomated insulin delivery, and that would at least improve their blood sugars overnight, and they would benefit," Gabbay said.

CMS approved external insulin pumps for T1D and T2D Medicare patients who had been on multiple daily injections (and who have less control as they learn to use the pump in the first year), Hodorowicz noted. "The cost benefit has to be there for CMS to approve coverage for such an expensive item," she said.

When asked about the differences between models and patient preferences, Hodorowicz said that a waterproof device is important to many patients. Some devices are disposable; some offer wireless infusion versus manual control. Different types of alarms matter to patients, as does ease of calibration. "I think the ease factor is critical," she said.

CGM devices are on the verge of becoming much smaller and cheaper, Gabbay said, although pumps may remain relatively expensive and complex. Snow noted a possible disconnect between what makes sense from an individual's point of view versus the population perspective. Giving an expensive device to a patient with a high glycated hemoglobin who seems unmotivated and unengaged may not make sense, but if a person's A1C of 10% drops by 1.5%, then the population has become healthier overall.

A person with T2D with poor control could benefit from a continuous glucose monitor, Kaufman said, by identifying personal patterns and seeing the connection between certain foods and spikes in blood glucose. "The question becomes, can it become a behavior-change incentive to allow you to become even better at managing your own condition?" he said.

The panel discussed an agreement that will require most adult UnitedHealth patients with diabetes to transition to Medtronic pumps and CGM devices as warranties expire.[10] "Sadly," Gabbay said, "it's somewhat inevitable because there will be competition around price, the same kind of things that happen in the pharmacy world—I don't see why it won't happen in the device world."

Snow said that historically, if 2 drugs have equal efficacy but 1 is cheaper, the savings are passed down the line and ultimately result in lower premiums. "Clearly, there can be a benefit without a detriment of care," he said.

Scanlon asked if payment models would change in this area, too. "Without a doubt," Snow said. "It is the direction of the payer industry." Many pharmaceutical companies have entered these agreements, "and the device companies are looking that way, as well," he said.

"The idea of just paying for your treatment is one that was there in the past, but more and more the question is: is there a value from your drug, from your device? Regardless of what it is, is it adding value in terms of either less expensive care or better care? And it doesn't have to be both."

Gabbay added that A1C is no longer the only measure of success. "If you reduce hypoglycemic episodes, well, that's probably a good thing, and that should be a metric, as well."

The field of diabetes technology has entered an exciting era, Kaufman said. "A paradigm shift is happening," he said. "We've got consumerism, where individuals are taking more control and responsibility for many things, including their health and health care. We've got technology being able to deliver something in the moment. You have it in your pocket at all times.

"We've got the concept of population health, the concept of value-based care coming to a health system that wasn't set up that way. If the patient is at the center, we always think of them as what's most important and their needs, that we, as healthcare providers and payers and employers and health systems, will make it so that we'll help patients have those outcomes that they need." ■

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INDICATION AND LIMITATION OF USE

†JARDIANCE is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.

JARDIANCE is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

JARDIANCE is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

JARDIANCE should not be used in patients with a history of serious hypersensitivity to JARDIANCE or in patients with severe renal impairment, end-stage renal disease, or dialysis.

Hypotension

JARDIANCE causes intravascular volume contraction and symptomatic hypotension may occur. Before initiating JARDIANCE, assess and correct volume status in the elderly, in patients with renal impairment, low systolic blood pressure, or on diuretics. Monitor for hypotension.

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co transporter 2 (SGLT2) inhibitors, including JARDIANCE. Fatal cases of ketoacidosis have been reported in patients taking JARDIANCE. Patients who present with signs and symptoms of metabolic acidosis should be assessed for ketoacidosis, even if blood glucose levels are less than 250 mg/dL. If suspected, discontinue JARDIANCE, evaluate and treat promptly.

Before initiating JARDIANCE, consider risk factors for ketoacidosis. Patients on JARDIANCE may require monitoring and temporary discontinuation in situations known to predispose to ketoacidosis.

Please see Important Safety Information and Brief Summary of Prescribing Information on adjacent pages.

LIFESAVING CV BENEFIT†

*Patients with coronary artery disease, peripheral artery disease, or a history of myocardial infarction or stroke.
CV=cardiovascular.

Boehringer Ingelheim

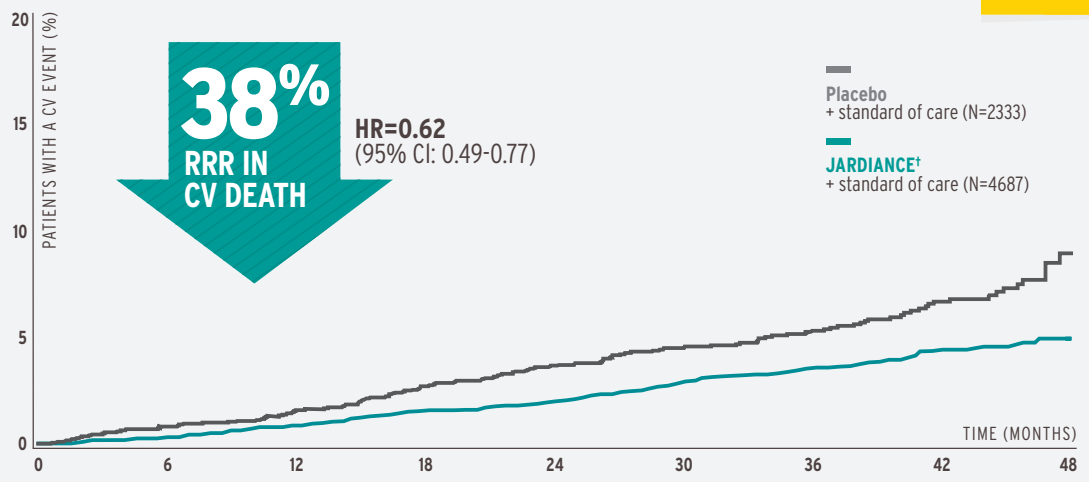
Lilly

FOR ADULTS WITH TYPE 2 DIABETES AND ESTABLISHED CV DISEASE

JARDIANCE powerfully reduced the risk of CV death on top of standard of care*

A consistent finding for the two JARDIANCE dosing strengths, 10 mg and 25 mg

REDUCED RISK OF CV DEATH



Absolute rates for CV death
3.7% JARDIANCE
VS 5.9% placebo

2.2%
ABSOLUTE RISK REDUCTION

EARLY AND SUSTAINED REDUCTIONS IN CV DEATH[1]

JARDIANCE DEMONSTRATED A 14% RRR FOR THE PRIMARY COMPOSITE ENDPOINT (p=0.04)

- **The absolute risk reduction for the composite endpoint was 1.6%**
- **There was no change in risk of nonfatal MI (HR=0.87 [95% CI: 0.70-1.09]) or nonfatal stroke (HR=1.24 [95% CI: 0.92-1.67]); the 14% RRR in CV events was due to a reduction in the risk of CV death (HR=0.62 [95% CI: 0.49-0.77])**

*Glucose-lowering and CV medications.

†Pooled data from JARDIANCE 10 mg and JARDIANCE 25 mg; similar magnitude of reduction was shown with both doses.

CI=confi dence interval; HR=hazard ratio; MI=myocardial infarction; RRR=relative risk reduction.

Study Design: A randomized, double-blind, parallel-group trial comparing the risk of experiencing a major adverse cardiovascular event between JARDIANCE and placebo when these were added to and used concomitantly with standard of care treatments for type 2 diabetes and cardiovascular disease. A total of 7020 patients were treated (JARDIANCE 10 mg [N=2345]; JARDIANCE 25 mg [N=2342]; placebo [N=2333]) and followed for a median of 3.1 years. All patients had established atherosclerotic cardiovascular disease at baseline, including one or more of the following: a documented history of coronary artery disease, stroke, or peripheral artery disease. The primary outcome was reduction in risk of cardiovascular events, defi ned by the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Acute Kidney Injury and Impairment in Renal Function

JARDIANCE causes intravascular volume contraction and can cause renal impairment. Acute kidney injury requiring hospitalization and dialysis have been identified in patients taking SGLT2 inhibitors, including JARDIANCE; some reports involved patients younger than 65 years of age. Before initiating JARDIANCE, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporary discontinuation in settings of reduced oral intake or fluid losses. Monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue JARDIANCE promptly and institute treatment.

JARDIANCE increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function should be evaluated prior to initiating JARDIANCE and periodically thereafter. More frequent monitoring is recommended in patients with eGFR <60 mL/min/1.73 m^2. JARDIANCE should be discontinued in patients with a persistent eGFR <45 mL/min/1.73 m^2.

Urosepsis and Pyelonephritis

Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been identified in patients receiving SGLT2 inhibitors, including JARDIANCE. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate for signs and symptoms of urinary tract infections and treat promptly.

Please see Important Safety Information and Brief Summary of Prescribing Information on adjacent pages.

FOR ADULTS WITH TYPE 2 DIABETES AND ESTABLISHED CV DISEASE

Jardiance® (empagliflozin) tablets 10 mg/25 mg

JARDIANCE offers protection against the risk of CV death on top of standard of care

THE ONLY FDA-APPROVED
type 2 diabetes medication indicated to reduce the risk of CV death

38%
RRR IN CV DEATH
vs placebo on top of standard of care
2.2% absolute risk reduction
HR=0.62 (95% CI: 0.49-0.77)

CONVENIENT ORAL DOSING
taken once daily in the morning

Learn more at JARDIANCEhcp.com

Reference: 1. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. *N Engl J Med*. 2015;373(22):2117-2128.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
Insulin and insulin secretagogues are known to cause hypoglycemia. The use of JARDIANCE with these agents can increase the risk of hypoglycemia. A lower dose of insulin or the insulin secretagogue may be required when used in combination with JARDIANCE.

Genital Mycotic Infections
JARDIANCE increases the risk for genital mycotic infections, especially in patients with prior infections. Monitor and treat as appropriate.

Increased Low-Density Lipoprotein Cholesterol (LDL-C)
Monitor and treat as appropriate.

ADVERSE REACTIONS
The most common adverse reactions (>5%) associated with placebo and JARDIANCE 10 mg and 25 mg were urinary tract infections and female genital mycotic infections.

DRUG INTERACTIONS
Diuretics may enhance the potential for volume depletion when administered with JARDIANCE.

USE IN SPECIAL POPULATIONS

Pregnancy
JARDIANCE is not recommended during the second and third trimesters of pregnancy based on animal data showing adverse renal effects.

Lactation
JARDIANCE is not recommended while breastfeeding because of the potential for serious adverse reactions in breastfed infants.

Geriatric Use
JARDIANCE is expected to have diminished efficacy in elderly patients with renal impairment. Urinary tract infections and volume depletion-related adverse reactions increased in patients ≥75 years treated with JARDIANCE.

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Please see Important Safety Information and Brief Summary of Prescribing Information on adjacent pages.

Boehringer Ingelheim

Lilly

JARDIANCE® (empagliflozin) tablets, for oral use

R_x only

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE: JARDIANCE is indicated: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus; to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. Limitations of Use: JARDIANCE is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS: History of serious hypersensitivity reaction to JARDIANCE; Severe renal impairment, end-stage renal disease, or dialysis *[see Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS: Hypotension: JARDIANCE causes intravascular volume contraction. Symptomatic hypotension may occur after initiating JARDIANCE *[see Adverse Reactions]* particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating JARDIANCE, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected *[see Use in Specific Populations]*. **Ketoacidosis:** Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including JARDIANCE. Fatal cases of ketoacidosis have been reported in patients taking JARDIANCE. JARDIANCE is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage]*. Patients treated with JARDIANCE who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with JARDIANCE may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, JARDIANCE should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement. In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified. Before initiating JARDIANCE, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with JARDIANCE consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery). **Acute Kidney Injury and Impairment in Renal Function:** JARDIANCE causes intravascular volume contraction *[see Warnings and Precautions (5.1)]* and can cause renal impairment *[see Adverse Reactions (6.1)]*. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including JARDIANCE; some reports involved patients younger than 65 years of age. Before initiating JARDIANCE, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing JARDIANCE in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue JARDIANCE promptly and institute treatment. JARDIANCE increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating JARDIANCE *[see Adverse Reactions (6.1)]*. Renal function should be evaluated prior to initiation of JARDIANCE and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2. Use of JARDIANCE is not recommended when eGFR is persistently less than 45 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.2), Contraindications (4), Use in Specific Populations (8.6)]*. **Urosepsis and Pyelonephritis:** There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including JARDIANCE. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions]*. **Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when JARDIANCE is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin *[see Adverse Reactions]*. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with JARDIANCE. **Genital Mycotic Infections:** JARDIANCE increases the risk for genital mycotic infections *[see Adverse Reactions]*. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Monitor and treat as appropriate. **Increased Low-Density Lipoprotein Cholesterol (LDL-C):** Increases in LDL-C can occur with JARDIANCE *[see Adverse Reactions]*. Monitor and treat as appropriate.

ADVERSE REACTIONS: The following important adverse reactions are described below and elsewhere in the labeling: Hypotension *[see Warnings and Precautions]*; Ketoacidosis *[see Warnings and Precautions)]*; Acute Kidney Injury and Impairment in Renal Function *[see Warnings and Precautions]*; Urosepsis and Pyelonephritis *[see Warnings and Precautions)]*; Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*; Genital Mycotic Infections *[see Warnings and Precautions]*; Increased Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions]*. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Pool of Placebo-Controlled Trials evaluating JARDIANCE 10 and 25 mg: The data in Table 1 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with insulin. JARDIANCE was used as monotherapy in one trial and as add-on therapy in four trials. These data reflect exposure of 1976 patients to JARDIANCE with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), JARDIANCE 10 mg (N=999), or JARDIANCE 25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 m^2). Table 1 shows common adverse reactions (excluding hypoglycemia) associated with the use of JARDIANCE. The adverse reactions were not present at baseline, occurred more commonly on JARDIANCE than on placebo and occurred in greater than or equal to 2% of patients treated with JARDIANCE 10 mg or JARDIANCE 25 mg.

Table 1: Adverse Reactions Reported in ≥2% of Patients Treated with JARDIANCE and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of JARDIANCE Monotherapy or Combination Therapy

	Number (%) of Patients		
	Placebo N=995	JARDIANCE 10 mg N=999	JARDIANCE 25 mg N=977
Urinary tract infection[a]	7.6%	9.3%	7.6%
Female genital mycotic infections[b]	1.5%	5.4%	6.4%
Upper respiratory tract infection	3.8%	3.1%	4.0%
Increased urination[c]	1.0%	3.4%	3.2%
Dyslipidemia	3.4%	3.9%	2.9%
Arthralgia	2.2%	2.4%	2.3%
Male genital mycotic infections[d]	0.4%	3.1%	1.6%
Nausea	1.4%	2.3%	1.1%

[a]Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

[b]Female genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), JARDIANCE 10 mg (N=443), JARDIANCE 25 mg (N=420).

[c]Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia

[d]Male genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), JARDIANCE 10 mg (N=556), JARDIANCE 25 mg (N=557).

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. *Volume Depletion:* JARDIANCE causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg respectively. JARDIANCE may increase the risk of hypotension in patients at risk for volume contraction *[see Warnings and Precautions and Use in Specific Populations]*. *Increased Urination:* In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on JARDIANCE than on placebo (see Table 1). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. *Acute Impairment in Renal Function:* Treatment with JARDIANCE was associated with increases in serum creatinine and decreases in eGFR (see Table 2). Patients with moderate renal impairment at baseline had larger mean changes. *[see Warnings and Precautions* and *Use in Specific Populations]*. In a long-term cardiovascular outcome trial, the acute impairment in renal function was observed to reverse after treatment discontinuation suggesting acute hemodynamic changes play a role in the renal function changes observed with empagliflozin.

Table 2: Changes from Baseline in Serum Creatinine and eGFR[a] in the Pool of Four 24-week Placebo-Controlled Studies and Renal Impairment Study

		Pool of 24-Week Placebo-Controlled Studies		
		Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
Baseline Mean	N	825	830	822
	Creatinine (mg/dL)	0.84	0.85	0.85
	eGFR (mL/min/1.73 m^2)	87.3	87.1	87.8
Week 12 Change	N	771	797	783
	Creatinine (mg/dL)	0.00	0.02	0.01
	eGFR (mL/min/1.73 m^2)	-0.3	-1.3	-1.4
Week 24 Change	N	708	769	754
	Creatinine (mg/dL)	0.00	0.01	0.01
	eGFR (mL/min/1.73 m^2)	-0.3	-0.6	-1.4

Table 2 (Cont'd)		Moderate Renal Impairment[b]		
		Placebo		JARDIANCE 25 mg
Baseline Mean	N	187	–	187
	Creatinine (mg/dL)	1.49	–	1.46
	eGFR (mL/min/1.73 m^2)	44.3	–	45.4
Week 12 Change	N	176	–	179
	Creatinine (mg/dL)	0.01	–	0.12
	eGFR (mL/min/1.73 m^2)	0.1	–	-3.8
Week 24 Change	N	170	–	171
	Creatinine (mg/dL)	0.01	–	0.10
	eGFR (mL/min/1.73 m^2)	0.2	–	-3.2
Week 52 Change	N	164	–	162
	Creatinine (mg/dL)	0.02	–	0.11
	eGFR (mL/min/1.73 m^2)	-0.3	–	-2.8
Post-treatment Change[c]	N	98	–	103
	Creatinine (mg/dL)	0.03	–	0.02
	eGFR (mL/min/1.73 m^2)	0.16	–	1.48

[a]Observed cases on treatment.
[b]Subset of patients from renal impairment study with eGFR 30 to less than 60 mL/min/1.73 m^2
[c]Approximately 3 weeks after end of treatment.

Hypoglycemia: The incidence of hypoglycemia by study is shown in Table 3. The incidence of hypoglycemia increased when JARDIANCE was administered with insulin or sulfonylurea *[see Warnings and Precautions]*.

Table 3: Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Studies[c]

Monotherapy (24 weeks)	**Placebo (n=229)**	**JARDIANCE 10 mg (n=224)**	**JARDIANCE 25 mg (n=223)**
Overall (%)	0.4%	0.4%	0.4%
Severe (%)	0%	0%	0%
In Combination with Metformin (24 weeks)	**Placebo + Metformin (n=206)**	**JARDIANCE 10 mg + Metformin (n=217)**	**JARDIANCE 25 mg + Metformin (n=214)**
Overall (%)	0.5%	1.8%	1.4%
Severe (%)	0%	0%	0%
In Combination with Metformin + Sulfonylurea (24 weeks)	**Placebo (n=225)**	**JARDIANCE 10 mg + Metformin + Sulfonylurea (n=224)**	**JARDIANCE 25 mg + Metformin + Sulfonylurea (n=217)**
Overall (%)	8.4%	16.1%	11.5%
Severe (%)	0%	0%	0%
In Combination with Pioglitazone +/- Metformin (24 weeks)	**Placebo (n=165)**	**JARDIANCE 10 mg + Pioglitazone +/- Metformin (n=165)**	**JARDIANCE 25 mg + Pioglitazone +/- Metformin (n=168)**
Overall (%)	1.8%	1.2%	2.4%
Severe (%)	0%	0%	0%
In Combination with Basal Insulin +/- Metformin (18 weeks[d])	**Placebo (n=170)**	**JARDIANCE 10 mg (n=169)**	**JARDIANCE 25 mg (n=155)**
Overall (%)	20.6%	19.5%	28.4%
Severe (%)	0%	0%	1.3%
In Combination with MDI Insulin +/- Metformin (18 weeks[d])	**Placebo (n=188)**	**JARDIANCE 10 mg (n=186)**	**JARDIANCE 25 mg (n=189)**
Overall (%)	37.2%	39.8%	41.3%
Severe (%)	0.5%	0.5%	0.5%

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose
[c]Treated set (patients who had received at least one dose of study drug)
[d]Insulin dose could not be adjusted during the initial 18 week treatment period

Genital Mycotic Infections: In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with JARDIANCE compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either JARDIANCE 10 or 25 mg. Genital mycotic infections occurred more frequently in female than male patients (see Table 1). Phimosis occurred more frequently in male patients treated with JARDIANCE 10 mg (less than 0.1%) and JARDIANCE 25 mg (0.1%) than placebo (0%). *Urinary Tract Infections:* In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with JARDIANCE compared to placebo (see Table 1). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Warnings and Precautions and Use in Specific Populations]*. *Laboratory Tests:* Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with JARDIANCE. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively *[see Warnings and Precautions]*. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups. Increase in Hematocrit: In a pool of four placebo-controlled studies, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in JARDIANCE 10 mg and 2.8% in JARDIANCE 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. **Postmarketing Experience:** Additional adverse reactions have been identified during postapproval use of JARDIANCE. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Ketoacidosis *[see Warnings and Precautions]*; Urosepsis and pyelonephritis *[see Warnings and Precautions]*.

DRUG INTERACTIONS: Diuretics: Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion *[see Warnings and Precautions]*. **Insulin or Insulin Secretagogues:** Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia *[see Warnings and Precautions]*. **Positive Urine Glucose Test:** Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control. **Interference with 1,5-anhydroglucitol (1,5-AG) Assay:** Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Risk Summary:* Based on animal data showing adverse renal effects, JARDIANCE is not recommended during the second and third trimesters of pregnancy. Limited data available with JARDIANCE in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*. In animal studies, adverse renal changes were observed in rats when empagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible. Empagliflozin was not teratogenic in rats and rabbits up to 300 mg/kg/day, which approximates 48-times and 128-times, respectively, the maximum clinical dose of 25 mg when administered during organogenesis *[see Data]*. The estimated background risk of major birth defects is 6-10% in women with pregestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Clinical Considerations: *Disease-associated maternal and/or embryo/fetal risk:* Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity. *Data:* Animal Data: Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30 and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13 week drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48-times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose. In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16 times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4 times the 25 mg maximum clinical dose). **Lactation:** *Risk Summary:* There is no information regarding the presence of JARDIANCE in human milk, the effects of JARDIANCE on the breastfed infant or the effects on milk production. Empagliflozin is present in the milk of lactating rats *[see Data]*. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in a breastfed infant,

advise women that use of JARDIANCE is not recommended while breastfeeding. *Data:* Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 -5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. **Pediatric Use:** The safety and effectiveness of JARDIANCE in pediatric patients under 18 years of age have not been established. **Geriatric Use:** No JARDIANCE dosage change is recommended based on age. In studies assessing the efficacy of empagliflozin in improving glycemic control in patients with type 2 diabetes, a total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. JARDIANCE is expected to have diminished glycemic efficacy in elderly patients with renal impairment *[see Use in Specific Populations]*. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively *[see Warnings and Precautions and Adverse Reactions]*. **Renal Impairment:** The efficacy and safety of JARDIANCE were evaluated in a study of patients with mild and moderate renal impairment. In this study, 195 patients exposed to JARDIANCE had an eGFR between 60 and 90 mL/min/1.73 m^2, 91 patients exposed to JARDIANCE had an eGFR between 45 and 60 mL/min/1.73 m^2 and 97 patients exposed to JARDIANCE had an eGFR between 30 and 45 mL/min/1.73 m^2. The glucose lowering benefit of JARDIANCE 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function. In a large cardiovascular outcomes study, there were 1819 patients with eGFR below 60 mL/min/1.73 m^2. The cardiovascular death findings in this subgroup were consistent with the overall findings. The efficacy and safety of JARDIANCE have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. JARDIANCE is not expected to be effective in these patient populations *[see Contraindications and Warnings and Precautions]*. **Hepatic Impairment:** JARDIANCE may be used in patients with hepatic impairment.

OVERDOSAGE: In the event of an overdose with JARDIANCE, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied.

Additional information can be found at www.hcp.jardiance.com

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Can SGLT2 Inhibitors Prevent Heart Failure in a Broad Population?

Mary Caffrey

A study of nearly 365,000 patients taking medication for type 2 diabetes (T2D) has found that sodium glucose co-transporter-2 (SGLT2) inhibitors outperform other treatments for the disease in key ways—and may help prevent heart failure (HF) in patients with T2D not yet diagnosed.

Results from the study, called CVD-REAL, were first presented March 19, 2017, at the 66th Scientific Session of the American College of Cardiology (ACC).[1] (A related paper was published in May in *Circulation*.[2]) The study, which covered patients from the United States and 5 European countries, examined some questions left unanswered by the EMPA-REG OUTCOME study, which was the first cardiovascular outcomes trial (CVOT) that did not merely find that a T2D therapy was safe, but that it could offer cardioprotective benefits and reduce deaths.[3]

> **"Eighty-seven percent of the patients did not have predefined cardiovascular disease. This tells me we can apply the results to a much broader population."**
>
> *—Jim McDermott, PhD, vice president for Medical Affairs, AstraZeneca*

But because EMPA-REG OUTCOME was a safety trial required by the FDA, it studied high-risk patients, and it only examined 1 drug, empagliflozin (Jardiance). In an interview at ACC prior to presentation of the results, AstraZeneca's Jim McDermott, vice president for medical affairs, Diabetes, said CVD-REAL was designed to ask whether the effects on HF are a class effect for all SGLT2 inhibitors, if these effects could be applied to a broad population, and "if they can be demonstrated in a real-world environment." AstraZeneca funded the study.

Researchers in the CVD-REAL study gathered data from patients 1 of 3 approved SGLT2 inhibitors: dapagliflozin (Farxiga) from AstraZeneca; canagliflozin (Invokana) from Janssen; and empagliflozin from Boehringer-Ingelheim and Eli Lilly. They also matched data from patients taking other glucose-lowering therapies. Compared with other T2D drugs, the SGLT2 inhibitor class:

- Reduced the rate of hospitalization for HF by 39%
- Reduced the rate of death from any cause by 51%

Researchers also computed a composite endpoint of hospitalization for HF and death from any cause and found that SGLT2s inhibitors reduced this by 46% compared with other T2D therapies.

SGLT2 inhibitors work through a unique mechanism of action, which causes excess blood glucose to be expelled through urine. McDermott said this mechanism has been shown to have a diuretic effect that positively affects blood pressure (and has been shown to help patients lose weight), although this effect is not well understood.

EMPA-REG OUTCOME raised the curtain on potential new benefits that CVD-REAL sought to explore. Could SGLT2 inhibitors not only treat diabetes, but also prevent HF in these patients?

Mikhail Kosiborod, MD, the study's lead author and a cardiologist at St. Luke's Health System in Kansas City, Missouri, said in his presentation at ACC that the results suggest a "heart failure prevention signal," because so few of the study participants had been diagnosed with cardiovascular disease at baseline.

McDermott agreed. "Eighty-seven percent of the patients did not have predefined cardiovascular disease," he said. "This tells me we can apply the results to a much broader population."

The study did not include results by individual drug. Of the data reviewed for the HF analysis, 41.8% of patients were on dapagliflozin, 52.7% on canagliflozin, and 5.5% on empagliflozin. The US population was more heavily weighted with canagliflozin users, where it was approved first, while the European data had more dapagliflozin users. Because the results were so consistent across different countries, McDermott said, they point to a class effect.

CVD-REAL will continue with more countries participating, McDermott said. Besides the United States, the first study included Denmark, Norway, Sweden, the United Kingdom and Germany; future studies may include data from Canada, Mexico, and Japan.

The expense of CVOTs has raised the question whether data-driven studies, such as CVD-REAL, could be the wave of the future. But both McDermott, in the interview, and Kosiborod, in his presentation, said CVOTs remain extremely important. "We need more and more data from various sources," Kosiborod said. ■

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