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Evidence-Based Diabetes Management

IDEAS AND INNOVATION ISSUE

Clinical Trials

Can SGLT2 Inhibitors Offer Options for Type 1 Treatment?

ANDREW SMITH

Better insulin formulations and glucose monitors have significantly improved the control of type 1 diabetes (T1D). Large studies in various countries have found that average glycated hemoglobin (A1C) levels have fallen by more than half a percentage point since the 1990s,[1,2] and that the disease shortens lifespan far less than it once did.[3] Recent trials, moreover, have shown that sophisticated software can control the disease even better, at least in the short term, by continuously monitoring glucose levels using data to control the timing and precise amount of insulin treatment.[4]

Yet most patients with T1D still have elevated levels of A1C, and even those who do manage to keep their levels in the optimal range, below 7%, have significantly higher mortality rates than similar patients who don't have T1D.[5] Researchers, therefore, are looking for new tools to manage the disease, and many are looking hardest at medications developed to treat type 2 diabetes (T2D).

A class of drugs called sodium-glucose co-transporter 2 (SGLT2) inhibitors has attracted particular interest. Indeed, all 3 such drugs that are FDA-approved to treat T2D—dapagliflozin (Farxiga), canagliflozin (Invokana) and empagliflozin (Jardiance)—are under investigation for use in patients with T1D. This interest stems not only from the ability of SGLT2 inhibitors to reduce A1C levels, but also from their documented tendency to promote weight loss and moderate short-term fluctua-

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Pharmacy Update

Could Patiromer Change the Face of Treatment for Patients With Diabetic Renal Disease?

ERIN DREWNIANY

The prevalence of diabetes, whether type 1 or type 2, continues to increase at a rapid pace worldwide. According to the American Diabetes Association, the worldwide prevalence of diabetes in 2010 was estimated at 6.4%, affecting 285 million individuals. That percentage is projected to increase by 2030 to 7.7%, affecting 439 million individuals across the world.[1] Diabetes can bring with it other health complications, which can drastically impact everyday life. Hypertension, heart disease, and kidney failure are the more common serious comorbidities. The good news is that with all these disease states, including diabetes, there are a number of efficacious drug regimens that can keep patients healthy and slow disease progression.

Management of diabetic renal disease, referred to as diabetic nephropathy, plays a critical role in increasing the survival rate of patients in this demographic. Diabetic nephropathy is defined as diabetes with the presence of microalbuminuria, which can increase risk of death due to heart disease.[2] Studies suggest that 30% of patients with type 1 diabetes are affected by kidney disease, while 20% with type 2 diabetes are affected.[2] When it comes to kidney disease, with or without diabetes, it is extremely important to keep any comorbidities under control; this requires monitoring blood pressure,

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Technology

Diabetes Management: *An Age-Old Problem That Needs a Modern Day Solution*

FRANCOIS NICOLAS, PHD

Since the discovery of insulin in 1921, there has been significant progress in the diagnosis and treatment of diabetes, but clinical outcomes for people living with diabetes still remain less-than-ideal. Despite a plethora of treatments available, only half of the people with diabetes are at their target glycated hemoglobin (A1C) level,[1] the standard measure for diabetes management. And, if left uncontrolled, many people experience 1 or more associated complications, including kidney disease, heart disease, stroke, blindness, and amputations, all of which come with a high price tag. In the United States alone, the annual cost of diabetes approaches $245 billion.[2] Nearly two-thirds of the $176 billion of direct medical costs is for hospitalizations and medications to treat complications.[3] Overall, medical costs alone are twice as high for individuals with diabetes than those without the disease.[2]

The time to address this tremendous personal and societal burden is now. Without new solutions, the problems associated with diabetes will only get worse. According to the International Diabetes Federation, by the year 2035, the number of people affected by diabetes worldwide is expected to climb to nearly 600 million, up from 400 million today.[4]

Despite this bleak landscape, there is hope from the positive results of numerous clinical trials showing the effectiveness of behavioral interven-

(continued on page SP533)

SOCIAL MEDIA AND DIABETES

Three well-known participants in the diabetes online community offer a commentary on the value of social media and call for more research to measure its health benefits (**SP515**).

Also in this issue...

Toujeo®

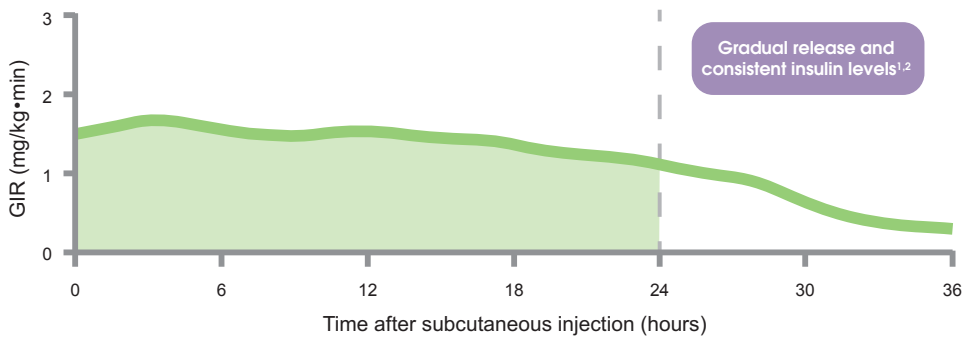
insulin glargine injection 300 Units/mL

An Insulin of Today

A stable activity profile[a] to last beyond 24 hours[1]

Once-daily Toujeo® should be injected at the same time each day.

A different distribution profile than an equivalent dose of Lantus® (insulin glargine injection) 100 Units/mL[1]



1/3 the injection volume of standard insulin (100 Units/mL)[1]

GIR=glucose infusion rate.

[a]The pharmacodynamics of Toujeo® at steady state after 8 days of daily injections was evaluated against Lantus® in a euglycemic clamp study of patients with type 1 diabetes mellitus (T1DM) (N=30). The dose on day 8 was followed by a 36-hour euglycemic clamp.[1,3]

- Toujeo® at steady state had a different activity profile than an equivalent dose of Lantus®, with a 27% lower GIR as measured by the 24-hour area under the curve[1]
- Steady-state levels are reached by at least 5 days of once-daily injections[1]
- Patients on Toujeo® may require a 10%-18% higher dose than patients on Lantus®[1]

Indications and Usage for Toujeo® (insulin glargine injection) 300 Units/mL

Toujeo® is a long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus.

Limitations of Use: Toujeo® is not recommended for treating diabetic ketoacidosis.

Please see additional Important Safety Information for Toujeo® on the following pages.

Please see brief summary of full Prescribing Information for Toujeo® on the following pages.

Important Safety Information for Toujeo® (insulin glargine injection) 300 Units/mL

Contraindications

Toujeo® is contraindicated during episodes of hypoglycemia and in patients hypersensitive to insulin glargine or any of its excipients.

Warnings and Precautions

Toujeo® contains the same active ingredient, insulin glargine, as Lantus®. The concentration of insulin glargine in Toujeo® is 300 units per mL.

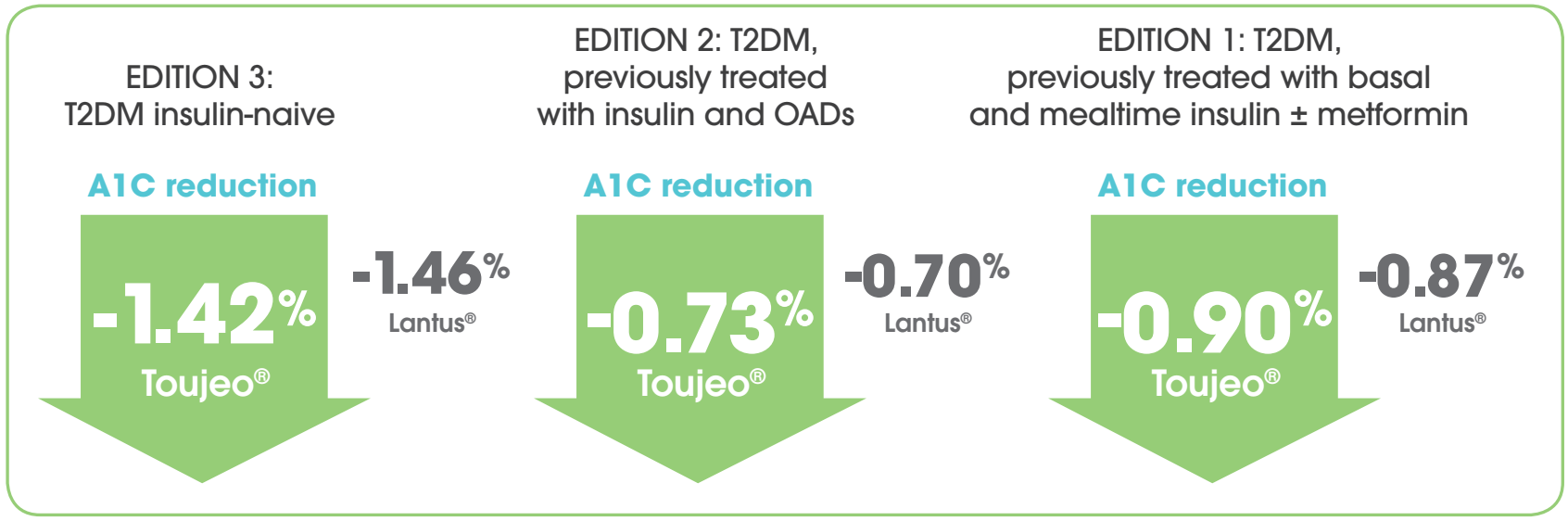
Insulin pens and needles must never be shared between patients. Do NOT reuse needles.

Toujeo® offers today's adult patients who require basal insulin:

- Small precipitate and gradual release[1,2]
- A1C: Reductions in a broad range of adult patients with diabetes[1,b]
- Proven safety profile[1]
- Redesigned pen
- Toujeo® COACH—tailored, integrated patient support

[b]Based on their previous anti-hyperglycemic therapy.

Toujeo® provides consistent and significant A1C reductions in a once-daily dose[1,c]



- In all studies Toujeo® met the primary endpoint (prespecified noninferiority margin of 0.4% and a 95% CI)[1,4]

[c]All studies were 26-week, open-label, controlled, titrate-to-target, noninferiority studies in adults with diabetes not at A1C goal (range: 7% to 10% or 11%), randomized to Toujeo® or Lantus® once daily. All patients were titrated to an FPG goal of 80-100 mg/dL. In EDITION 1, patients used Toujeo® with mealtime insulin analog ± metformin. In EDITION 2 and 3, patients used Toujeo® with OADs.
T2DM=type 2 diabetes mellitus; OAD=oral antidiabetes drugs; FPG=fasting plasma glucose.

Incidence of hypoglycemia in T2DM studies[1]	
Severe,[d] Toujeo® with OADs regimen	0.9% to 1.0%
Severe,[d] Toujeo® with mealtime insulin regimen	5%
Documented symptomatic hypoglycemia in multiple studies[e,f]	8% to 37%

[d]Severe hypoglycemia: event requiring assistance of another person to actively administer a resuscitative action.

[e]Documented symptomatic hypoglycemia: an event with typical symptoms of hypoglycemia accompanied by a self-monitored plasma glucose value ≤54 mg/dL.

[f]Toujeo® with OADs or with mealtime insulin regimen with or without metformin.

- Most common adverse events with Toujeo® in T2DM patients: 7.1% nasopharyngitis, 5.7% upper respiratory infection

Visit www.toujeopro.com for more information.

References
1. Toujeo® Prescribing Information. May 2015. **2.** Maiorino MI, et al. *Expert Opin Biol Ther.* 2014; 14(6):799-808.
3. Becker RHA, Dahmen R, et al. *Diabetes Care.* 2015;38(4):637-643. **4.** Data on file, Sanofi US.

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Toujeo®
insulin glargine injection 300 Units/mL

Important Safety Information for Toujeo® (insulin glargine injection) 300 Units/mL

Warnings and Precautions (cont'd)

Monitor blood glucose in all patients treated with insulin. Modify insulin regimens cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose or an adjustment in concomitant oral antidiabetic treatment. Changes in insulin regimen may result in hyperglycemia or hypoglycemia.

Unit for unit, patients started on, or changed to, Toujeo® required a higher dose than patients controlled with Lantus®. When changing from another basal insulin to Toujeo®, patients experienced higher average fasting plasma glucose levels in the first few weeks of therapy until titrated to their individualized fasting plasma glucose targets. Higher doses were required in titrate-to-target studies to achieve glucose control similar to Lantus®.

Hypoglycemia is the most common adverse reaction of insulin therapy, including Toujeo®, and may be life-threatening.

Medication errors such as accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. Patients should be instructed to always verify the insulin label before each injection.

Do not dilute or mix Toujeo® with any other insulin or solution. If mixed or diluted, the solution may become cloudy, and the onset of action/time to peak effect may be altered in an unpredictable manner. Do not administer Toujeo® via an insulin pump or intravenously because severe hypoglycemia can occur.

Severe life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue Toujeo®, monitor and treat if indicated.

A reduction in the Toujeo® dose may be required in patients with renal or hepatic impairment.

As with all insulins, Toujeo® use can lead to life-threatening hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Closely monitor potassium levels in patients at risk of hypokalemia and treat if indicated.

Fluid retention, which may lead to or exacerbate heart failure, can occur with concomitant use of thiazolidinediones (TZDs) with insulin. These patients should be observed for signs and symptoms of heart failure. If heart failure occurs, dosage reduction or discontinuation of TZD must be considered.

Drug Interactions

Certain drugs may affect glucose metabolism, requiring insulin dose adjustment and close monitoring of blood glucose. The signs of hypoglycemia may be reduced in patients taking anti-adrenergic drugs (eg, beta-blockers, clonidine, guanethidine, and reserpine).

Adverse Reactions

Adverse reactions commonly associated with Toujeo® include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema and weight gain.

Important Safety Information for Toujeo® SoloStar®

Toujeo® SoloStar® is a disposable prefilled insulin pen. To help ensure an accurate dose each time, patients should follow all steps in the Instruction Leaflet accompanying the pen; otherwise they may not get the correct amount of insulin, which may affect their blood glucose levels.

Do not withdraw Toujeo® from the SoloStar® disposable prefilled pen with a syringe.

Please see Brief Summary of Prescribing Information on the following pages.

References: 1. Toujeo Prescribing Information. May 2015. **2.** Becker RHA, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T. *Diabetes Care.* 2015;38(4):637-643. **3.** Data on file, Sanofi US.

Brief Summary

TOUJEO® **Rx Only**
(insulin glargine injection) U-300, for subcutaneous use

Brief Summary of Prescribing Information

1. INDICATIONS AND USAGE

TOUJEO is indicated to improve glycemic control in adults with diabetes mellitus.

Limitations of Use

TOUJEO is not recommended for the treatment of diabetic ketoacidosis.

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

- Inject TOUJEO subcutaneously once a day into the abdominal area, thigh, or deltoid at the same time each day.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy *[See Adverse Reactions (6.1)]*.
- Individualize and titrate the dosage of TOUJEO based on the individual's metabolic needs, blood glucose monitoring results, and glycemic control goal. The dosage of TOUJEO ranges from 1 to 80 units per one injection.
- To minimize the risk of hypoglycemia titrate the dose of TOUJEO no more frequently than every 3 to 4 days.
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia *[see Warnings and Precautions (5.2), and Use in Specific Populations (8.5, 8.6)]*.
- To minimize the risk of hypoglycemia, do not administer TOUJEO intravenously, intramuscularly or in an insulin pump.
- To minimize the risk of hypoglycemia, do not dilute or mix TOUJEO with any other insulin products or solutions.

2.2 Starting Dose in Insulin-Naïve Patients

Type 1 Diabetes:

- The recommended starting dose of TOUJEO in insulin naïve patients with type 1 diabetes is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be given as a short-acting insulin and divided between each daily meal. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin naïve patients with type 1 diabetes.
- The maximum glucose lowering effect of a dose of TOUJEO may take five days to fully manifest and the first TOUJEO dose may be insufficient to cover metabolic needs in the first 24 hours of use [*See Clinical Pharmacology (12.2) in the full prescribing information*]. To minimize risks associated with insufficient insulinization when initiating TOUJEO, monitor glucose daily, titrate TOUJEO per instructions, and adjust co-administered glucose lowering therapies per standard of care.

Type 2 Diabetes:

- The recommended starting dose of TOUJEO in insulin naïve patients with type 2 diabetes is 0.2 units per kilogram of body weight once daily. The dosage of other anti-diabetic drugs may need to be adjusted when starting TOUJEO to minimize the risk of hypoglycemia *[See Warnings and Precautions (5.3)]*.

2.3 Starting Dose in Patients with either Type 1 or Type 2 Diabetes Already on Insulin Therapy

- To minimize the risk of hypoglycemia when changing patients from a once daily long-acting or intermediate acting insulin product to TOUJEO, the starting dose of TOUJEO can be the same as the once daily long-acting dose. For patients controlled on LANTUS (insulin glargine, 100 units/mL) expect that a higher daily dose of TOUJEO will be needed to maintain the same level of glycemic control *[see Clinical Pharmacology (12.2) in the full prescribing information and Clinical Studies (14.1) in the full prescribing information]*.
- To minimize the risk of hypoglycemia when changing patients from twice-daily NPH insulin to once-daily TOUJEO, the recommended starting TOUJEO dose is 80% of the total daily NPH dosage.
- To minimize the risk of hyperglycemia when changing patients to TOUJEO, monitor glucose frequently in the first weeks of therapy titrate the dose of TOUJEO per instructions and the dose of other glucose lowering therapies per standard of care. *[See Warning and Precautions (5.2) and Clinical Pharmacology Section (12.2) in the full prescribing information].*

2.4 Important Administration Instructions

- Prior to initiation of TOUJEO, patients should be trained by their healthcare professional on proper use and injection technique. Training reduces the risk of administration errors such as needle sticks and incomplete dosing.
- Patient should follow the *Instructions for Use* to correctly use the pen device and administer TOUJEO.

Please see Brief Summary of full Prescribing Information for Toujeo® on the following pages.

- Patients should be informed that the dose counter of the TOUJEO SoloStar disposable prefilled pen shows the number of units of TOUJEO to be injected. The TOUJEO SoloStar prefilled pen has been specifically designed for TOUJEO, therefore no dose conversion is required *[Patient counseling information (17) in the full prescribing information]*.
- Patients should be instructed to visually inspect the TOUJEO solution for particulate matter and discoloration prior to administration and only use if the solution is clear and colorless with no visible particles.
- For single patient use only *[see Warnings and Precautions (5.1)]*.
- Refrigerate unused (unopened) TOUJEO SoloStar prefilled pens.

4. CONTRAINDICATIONS

TOUJEO is contraindicated:

- During episodes of hypoglycemia *[See Warnings and Precautions (5.3)]*.
- In patients with hypersensitivity to insulin glargine or one of its excipients *[See Warnings and Precautions (5.5)]*.

5. WARNINGS AND PRECAUTIONS

5.1 Never Share a TOUJEO SoloStar pen Between Patients

TOUJEO SoloStar disposable prefilled pens must never be shared between patients, even if the needle is changed. Pen sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia *[see Warnings and Precautions (5.3)]* or hyperglycemia. These changes should be made cautiously and only under close medical supervision, and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, dosage adjustments of concomitant oral anti-diabetic products may be needed.

On a unit to unit basis, TOUJEO has a lower glucose lowering effect than LANTUS *[See Clinical Pharmacology (12.2) in the full prescribing information]*. In clinical trials, patients who changed to TOUJEO from other basal insulins experienced higher average fasting plasma glucose levels in the first weeks of therapy compared to patients who were changed to LANTUS. To minimize the risk of hyperglycemia when initiating TOUJEO monitor glucose daily, titrate TOUJEO according to labeling instructions, and adjust co-administered glucose lowering therapies per standard of care *[See Dosage and Administration (2.2, 2.3)]*. Higher doses of TOUJEO were required to achieve similar levels of glucose control compared to LANTUS in clinical trials *[see Clinical Studies (14.1) in the full prescribing information]*.

The onset of action of TOUJEO develops over 6 hours following an injection. In type 1 diabetes patients treated with IV insulin, consider the longer onset of action of TOUJEO before stopping IV insulin. The full glucose lowering effect may not be apparent for at least 5 days *[See Dosage and Administration (2.2) and Clinical Pharmacology (12.2) in the full prescribing information]*.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulin, including TOUJEO. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving, or operating other machinery). Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) *[See Drug Interactions (7)]*, or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation.

As with all insulin preparations, the glucose lowering effect time course of TOUJEO may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature *[see Clinical Pharmacology (12.2) in the full prescribing information]*. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication *[see Drug Interactions (7)]*. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia *[see Use in Specific Populations (8.5, 8.6)]*.

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended. To minimize the risk of hypoglycemia do not administer TOUJEO intravenously, intramuscularly or in an insulin pump or dilute or mix TOUJEO with any other insulin products or solutions.

5.4 Medication Errors

Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors between TOUJEO and other insulins, instruct patients to always check the insulin label before each injection.

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including TOUJEO. If hypersensitivity reactions occur, discontinue TOUJEO; treat per standard of care and monitor until symptoms and signs resolve *[See Adverse Reactions (6)]*. TOUJEO is contraindicated in patients who have had hypersensitivity reactions to insulin glargine or other of the excipients *[See Contraindications (4)]*.

5.6 Hypokalemia

All insulin products, including TOUJEO, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including TOUJEO, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

6. ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia *[See Warnings and Precautions (5.3)]*
- Hypersensitivity and allergic reactions *[See Warnings and Precautions (5.5)]*
- Hypokalemia *[See Warnings and Precautions (5.6)]*

6.1 Clinical trial 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 actually observed in clinical practice.

The data in Table 1 reflect the exposure of 304 patients with type 1 diabetes to TOUJEO with mean exposure duration of 23 weeks. The type 1 diabetes population had the following characteristics: Mean age was 46 years and mean duration of diabetes was 21 years. Fifty five percent were male, 86% were Caucasian, 5 % were Black or African American and 5 % were Hispanic. At baseline, the mean eGFR was 82 mL/min/1.73m^2 and 35% of patients had eGFR≥90 mL/min/1.73m^2. The mean BMI was 28 kg/m^2. HbA1c at baseline was greater or equal to 8% in 58% of patients.

The data in Table 2 reflect the exposure of 1242 patients with type 2 diabetes to TOUJEO with mean exposure duration of 25 weeks. The type 2 diabetes population had the following characteristics: Mean age was 59 years and mean duration of diabetes was 13 years. Fifty three percent were male, 88% were Caucasian, 7% were Black or African American and 17% were Hispanic. At baseline, mean eGFR was 79 mL/min/1.73m^2 and 27% of patients had an eGFR≥90 mL/min/1.73m^2. The mean BMI was 35 kg/m^2. HbA1c at baseline was greater or equal to 8% in 66% of patients.

Common adverse reactions were defined as reactions occurring in ≥5% of the population studied.

Common adverse reactions occurring for TOUJEO-treated subjects during clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in Table 1 and Table 2, respectively. Hypoglycemia is discussed in a dedicated subsection below.

Table 1: Adverse reactions in two pooled clinical trials of 26 weeks and 16 weeks duration in adults with type 1 diabetes (with incidence ≥5%)

	TOUJEO + mealtime insulin*, % (n=304)
Nasopharyngitis	12.8
Upper respiratory tract infection	9.5

*″mealtime insulin″ refers to insulin glulisine, insulin lispro, or insulin aspart

Table 2: Adverse reactions in three pooled clinical trials of 26 weeks duration in adults with type 2 diabetes (with incidence ≥5%)

	TOUJEO*, % (n=1,242)
Nasopharyngitis	7.1
Upper respiratory tract infection	5.7

*one of the trials in type 2 diabetes included mealtime insulin

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including TOUJEO *[See Warnings and Precautions (5.3)]*. In the TOUJEO program, severe hypoglycemia was defined as an event requiring assistance of another person to administer a resuscitative action and documented symptomatic hypoglycemia was defined as an event with typical symptoms of hypoglycemia accompanied by a self-monitored or plasma glucose value equal to or less than 54 mg/dL.

The incidence of severe hypoglycemia in patients with type 1 diabetes receiving TOUJEO as part of a multiple daily injection regimen was 6.6% at 26 weeks. The incidence of documented symptomatic hypoglycemia was 69% at 26 weeks. There were no clinically important differences in hypoglycemia between TOUJEO and LANTUS among type 1 diabetes patients.

The incidence of severe hypoglycemia in patients with type 2 diabetes was 5% at 26 weeks in patients receiving TOUJEO as part of a multiple daily injection regimen, and 1.0% and 0.9% respectively at 26 weeks in the two studies where patients received TOUJEO as part of a basal-insulin only regimen. The incidence of documented symptomatic hypoglycemia in patients with type 2 diabetes receiving TOUJEO ranged from 8% to 37% at 26 weeks and the highest risk was again seen in patients receiving TOUJEO as part of a multiple daily injection regimen.

Insulin initiation and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Peripheral Edema

Insulin, including TOUJEO, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Lipodystrophy

Long-term use of insulin, including TOUJEO, can cause lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients and may affect insulin absorption *[see Dosage and Administration (2.1)].*

Weight gain

Weight gain has occurred with some insulin therapies including TOUJEO and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

Allergic Reactions

Some patients taking insulin therapy, including TOUJEO have experienced erythema, local edema, and pruritus at the site of injection. These conditions were usually self-limiting. Severe cases of generalized allergy (anaphylaxis) have been reported *[See Warnings and Precautions (5.5)].*

Cardiovascular Safety

No clinical studies to establish the cardiovascular safety of TOUJEO have been conducted. A cardiovascular outcomes trial, ORIGIN, has been conducted with LANTUS. It is unknown whether the results of ORIGIN can be applied to TOUJEO. The Outcome Reduction with Initial Glargine Intervention trial (i.e., ORIGIN) was an open-label, randomized, 12,537 patient study that compared LANTUS to standard care on the time to first occurrence of a major adverse cardiovascular event (MACE). MACE was defined as the composite of CV death, nonfatal myocardial infarction and nonfatal stroke. The incidence of MACE was similar between LANTUS and standard care in ORIGIN [Hazard Ratio (95% CI) for MACE; 1.02 (0.94, 1.11)]. In the ORIGIN trial, the overall incidence of cancer (all types combined) [Hazard Ratio (95% CI); 0.99 (0.88, 1.11)] or death from cancer [Hazard Ratio (95% CI); 0.94 (0.77, 1.15)] was also similar between treatment groups.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity.

In a 6-month study of type 1 diabetes patients, 79% of patients who received TOUJEO once daily were positive for anti-insulin antibodies (AIA) at least once during the study, including 62% that were positive at baseline and 44% of patients who developed anti-drug antibody [i.e., anti-insulin glargine antibody (ADA)] during the study. Eighty percent of the AIA positive patients on TOUJEO with antibody test at baseline, remained AIA positive at month 6.

In two 6-month studies in type 2 diabetes patients, 25% of patients who received TOUJEO once daily were positive for AIA at least once during the study, including 42% who were positive at baseline and 20% of patients who developed ADA during the study. Ninety percent of the AIA positive patients on TOUJEO with antibody test at baseline, remained AIA positive at month 6.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to TOUJEO with the incidence of antibodies in other studies or to other products, may be misleading.

7. DRUG INTERACTIONS

7.1 Drugs That May Increase the Risk of Hypoglycemia

The risk of hypoglycemia associated with TOUJEO use may be increased with antidiabetic agents, (ACE) inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is co-administered with these drugs.

7.2 Drugs That May Decrease the Blood Glucose Lowering Effect of TOUJEO

The glucose lowering effect of TOUJEO may be decreased when co-administered with atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isonazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline) and thyroid hormones. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is co-administered with these drugs.

7.3 Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TOUJEO

The glucose lowering effect of TOUJEO may be increased or decreased when co-administered with alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is co-administered with these drugs.

7.4 Drugs That May Affect Signs and Symptoms of Hypoglycemia

The signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.3)]* may be blunted when beta-blockers, clonidine, guanethidine, and reserpine are co-administered with TOUJEO.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes, insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking TOUJEO.

Human data

There are no clinical studies of the use of TOUJEO in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal data

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 50 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day). In rabbits, doses of 0.072 mg/kg/day, which is approximately 10 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day), were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

8.3 Nursing Mothers

Endogenous insulin is present in human milk; it is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when TOUJEO is administered to a nursing woman. Use of TOUJEO is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

The safety and effectiveness of TOUJEO have not been established in pediatric patients.

8.5 Geriatric Use

In controlled clinical studies, 30 of 304 (9.8%) TOUJEO treated patients with type 1 diabetes and 327 of 1242 (26.3%) TOUJEO treated patients with type 2 diabetes were ≥65 years of age, among them 2.0 % of the patients with type 1 and 3.0% of the patients with type 2 diabetes were ≥75 years of age. No overall differences in effectiveness and safety were observed in the subgroup analyses across the age groups.

Nevertheless, caution should be exercised when TOUJEO is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia *[See Warnings and Precautions (5.3), Adverse reactions (6) and Clinical Studies (14) in the full prescribing information].*

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of TOUJEO has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for TOUJEO in patients with hepatic impairment *[See Warnings and Precautions (5.3)].*

8.7 Renal Impairment

The effect of renal impairment on the pharmacokinetics of TOUJEO has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Frequent glucose monitoring and dose adjustment may be necessary for TOUJEO in patients with renal impairment *[See Warnings and Precautions (5.3)].*

8.8 Obesity

No overall differences in effectiveness and safety were observed in subgroup analyses based on BMI.

10. OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.6)].* Mild episodes of hypoglycemia can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or physical activity level may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

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For more than 50 years, Joslin Diabetes Center has awarded medals to long-term survivors of diabetes. From that tradition came a cohort of patients whose health histories, blood, and tissue samples are giving researchers insights into how to prevent complications of type 1 disease. For an interview about the study with Joslin's chief scientific officer, George King, MD, ***see SP517****.*

Photo courtesy of Joslin Diabetes Center.

In Diabetes, Innovation Is All Around Us


MIKE HENNESSY, SR

November is American Diabetes Month, which offers an opportunity to raise awareness about what it is like for the nearly 30 million people in this country who live with the disease. The month is also an opportunity to draw attention to partnerships and advances in research that offer hope. Researchers in United States and around the world are hard at work looking for a way to reverse the onset of diabetes and cures to its most devastating consequences.

Several articles in this issue of *Evidence-Based Diabetes Management* discuss work with stem-cell therapy, which is being studied to treat diabetic retinopathy or to arrest early-stage type 1 disease. Multiple immunoprevention strategies are being explored, with support from advocacy groups like JDRF and pharmaceutical firms like Janssen. For some time now, we've seen partnerships emerge between medical and consumer technology companies in diabetes—and now it's happening in pursuit of sharing information, as we see in Sanofi's partnership with Google.

One of the most promising new therapeutic classes used to treat type 2 diabetes—the SGLT2 inhibitors—are being tested in clinical trials as a treatment for those with type 1 disease. Best of all, we're listening and learning more from the people who live with diabetes 24/7 and we're doing so through social media. This issue features a commentary from 3 panelists who took part in our spring conference, Patient-Centered Diabetes Care, and wanted to share the themes of that meeting with our readers: social media is a powerful tool that is worthy of attention from the research community because it's changing the way people gain support and practical information, as well as changing the way device companies and the FDA learn.

This issue features a diverse set of ideas from the frontiers of what's happening in diabetes care—but it's just a start. To learn more, join us April 7-8, 2016, for the next installment of Patient-Centered Diabetes Care. We're meeting in Teaneck, New Jersey. For more information, visit http://www.ajmc.com/meetings/pcdc16. We hope you can join us.

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

EDITORIAL MISSION

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in diabetes management.

Evidence-Based Diabetes Management

Welcome to Dr Peter Amenta, Joslin's New President & CEO

ROBERT A. GABBAY, MD, PHD, FACP

ABOUT THE EDITOR IN CHIEF — Joslin Diabetes Center

ROBERT A. GABBAY, MD, PHD, FACP

Dr Gabbay is chief medical officer and senior vice president of Joslin Diabetes Center. He serves as editor in chief of *Evidence-Based Diabetes Management.*

There's plenty of excitement at Joslin Diabetes Center these days, and it starts right at the top: In early October, we welcomed Peter S. Amenta, MD, PhD, as our new president and CEO.

Dr Amenta is familiar to us as a longtime board member, and from there, he transitioned into working with us in a consulting capacity. It's safe to say, he knows Joslin very well. Dr Amenta spent the majority of his career at Robert Wood Johnson Medical School in New Jersey, now part of Rutgers University, including 8 years as Dean. During that time, Dr Amenta took part in the tremendous growth and reorganization of that institution—including restructuring clinical practice, building relationships with hospital affiliates, and creating a state-of-the-art electronic health record, all of which will serve us well here at Joslin.

He sees Joslin as a place that has always balanced a search for a cure with crucial work on disease management. Through research and superior clinical care comes innovation. "We are well-known as the place to go when you have diabetes; we care for a lot of the very difficult patients," Dr Amenta told *Evidence-Based Diabetes Management.*

In his own research, Dr Amenta is an expert anatomic pathologist, electron microscopist, and immunohistochemist. He has authored more than 100 peer-reviewed articles, chapters and abstracts; he serves on the editorial board of *Human Pathology* and is a reviewer for other journals.

In New Jersey, Dr Amenta oversaw the launch of a stem cell research institute. Work in this area, of course, is at the heart of the search for a cure for type 1 diabetes (T1D), one of the pillars of our work in Boston.

Joslin President and CEO Peter S. Amenta, MD, PhD

Joslin's research strengths are quite strong, he reports. From the work in the Immunobiology Section, which has developed a mouse model that develops an autoimmune disease similar to T1D; to the research into the regeneration of beta cells—which offer promise for patients with both type 1 and type 2 disease—to the work in the relationship between diabetes and cardiovascular disease, "We really have a nice balance," Dr Amenta said.

Of course, Joslin plays a leading role in changing the way care is delivered. Joslin has achieved the highest rating for an institution of its type from the National Committee on Quality Assurance, and when he arrived, Dr Amenta said he was committed to doing even more to improve efficiency, quality, and innovation in care devleiery.

"While Joslin is structurally small—just 7 floors—what we can do with our affiliates, with working with insurers and ACOs to improve the outcomes in diabetes—that's where we're looking to interact to make sure to deliver quality care that decreases costs," Dr Amenta said. "The more we decrease the need for patients to be in the hospital or the ER, the better." **EBDM**

Is It Possible to Prevent or Delay Type 1 Diabetes?

SEJAL SARAIYA, PHARMD

ABOUT THE EXPERT

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

RICHARD INSEL, MD

Dr Insel is the chief scientific officer of JDRF, where he oversees research strategy.

What if there was a way to determine exactly who would develop type 1 diabetes (T1D) and doctors could intervene to prevent it altogether or at least delay the onset by years?

JDRF, a leading research advocacy organization, and the Disease Interception Accelerator (DIA) group of Janssen Pharmaceuticals announced a joint venture earlier this year to take on this challenge.[1] The goal is to identify the root cause of T1D and intercept its progression to disease before symptoms arise.

There have been many questions about the actual cause of T1D. Work in recent years suggests there is a window of opportunity to stop or delay the disease before the onset of clinical symptoms of the disease.[2,3] The autoimmune response directed against beta cells is suggested to be secondary to tissue damage and unrelated to disease pathogenesis.[4] The presence of antibodies against the islets of Langerhans that were detected in the serum of patients diagnosed with T1D, but not in healthy individuals, led to the suggestion of the autoimmune etiology of T1D.[4]

Although T1D has been referred to by many names, such as juvenile diabetes or insulin-dependent diabetes, the treatment has always been the same: insulin. T1D is a pancreatic beta cell-specific disease that results in absolute insulin deficiency.[4,5] Data from the United Kingdom suggest life expectancy of adults with T1D is reduced by up to 13 years.[6,7] The symptoms of T1D are similar to type 2 diabetes, including frequent urination and feeling thirsty, hungry, or tired. Additionally, with T1D, there is the possibility of sudden weight loss, nausea and vomiting from the build-up of ketones in the body, and diabetic ketoacidosis.[8]

Although only about 5% of patients with diabetes have T1D,[9] the effect can be more devastating since children and young adults are the ones most commonly given a diagnosis of T1D. These individuals live with the disease for many more years, thus prolonging the time for cellular damage, which increases the potential for complications of diabetes that include blindness and kidney damage and, in extreme cases, loss of toes or lower limbs.[8] The goal of intensive insulin therapy is to reduce long-term complications while avoiding acute emergencies, such as hypoglycemia, to optimize quality of life for patients.[2,6]

DISEASE PATHOLOGY

T1D is mainly related to an autoimmune response through which the action of T cells and/or T lymphocytes results in destruction of pancreatic cells.[10] The most commonly identified islet autoantibodies associated with progression to T1D are insulin autoantibodies), glutamic acid decarboxylase 65 autoantibodies, insulinoma antigen 2 autoantibodies, and zinc transporter 8 autoantibodies.[11] However, T1D can also be triggered by different factors such as obesity, viruses, and chronic or acute inflammations that affect the cells of the pancreas that produce insulin.[10] Although there are no physical symptoms, there is data that suggests T1D is commonly preceded by early symptoms including seroconversion to islet autoantibody and metabolic disturbances.[11] The mechanism of how metabolic syndrome and autoimmune factors affect the progression of T1D is not yet clear, however.

POTENTIAL PREVENTION STRATEGIES

About 50% of patients with T1D are overweight or obese.[12] Whereas insulin therapy can achieve optimal glucose control, it can also cause patients to gain weight. This makes insulin less effective, which then requires more insulin—and a vicious cycle begins. Traditional treatment options for T1D include pancreas transplantation and transplant of islet and embryonic stem cells.

Pancreas transplantation[10] is still a useful treatment for some patients; however, it might not be an optimal option for all patients. Transplant of islet cells is an option, safer than transplantation, but still an invasive procedure.[10] Finally, embryonic stem cells are still in the research phase due to costs and standardization concerns.[10] These options are viable, but they should probably be used in patients with extreme disease progression or reserved as a last resort.

Adjunct therapies may be necessary to help better manage glucose levels and optimize insulin therapy,[12] thereby reducing T1D complications, preserving beta cells, and improving insulin secretion.[10] There is ongoing research for alternative treatments for continuous glycemic control and for slowing down the damage caused by T1D.[10] Studies have looked at the use of immunosuppressive agents, including cyclosporine, prednisone, and azathioprine, for initiating the remission of T1D.[4] Results suggest the preservation of residual beta cells, with adjunct immunosuppressants, was able to produce sufficient insulin and subsequently improve glycated hemoglobin. However, when treatment ended, T1D rapidly relapsed.[4,10] The big concern with using immunosuppressive agents is the toxicity associated with their use.[4]

JDRF's chief scientific officer, Richard Insel, MD, and his team are eager to work with Janssen's DIA group to advance an innovative scientific initiative.[1] Insel and JDRF are big advocates for preventive intervention; at the launch of the venture, Insel said it provides an exciting opportunity.[1]

"The studies are all still in the research setting," Insel said in an interview with *Evidence-Based Diabetes Management*. He shared the 2 main ways of identifying patients at risk of developing T1D. One involves screening relatives of patients with T1D for an autoimmune response, specifically identifying antibodies that would attack islets of pancreas cells. Several antibodies have previously been identified, and individuals who produce 2 or more islet autoantibodies are at a higher risk for developing T1D.[11] The progression to T1D, he said, could take years or even decades, however.

The second method of identifying patients at risk for developing T1D requires screening all children younger than 18 years. This would include a genetic-risk screening of children once a year, perhaps at the annual medical visit. This is already being done in Germany for all 3- and 4-year-olds. Insel referred to TrialNet, a T1D study conducted by an international network of researchers who are exploring ways to prevent, delay, and reverse the progression of disease.[13] The study presented by Alberto Pugliese, MD, in June 2014 at the 74th Scientific Sessions of the American Diabetes Association, was a 5-year study that followed relatives of patients who have T1D. In the study, researcher looked at the risk of developing T1D with human leukocyte antigen influence, in addition to having positive autoantibodies. The results showed that having several high-risk haplotypes/genotypes indicated a high risk for 5-year T1D incidence. Relatives with a single antibody had an increased risk of developing additional autoantibodies, without progression to T1D.[14]

Another article pooled data from several prospective cohort studies that examined children who were genetically at risk for developing T1D. The results showed an almost 70% risk of progression to T1D at a 10-year follow-up when patients had multiple islet autoantibodies compared with 15% for patients with a single autoantibody. Children who lacked islet autoantibodies had a less than 1% risk to progression.[15]

The Pre-POINT study, funded by JDRF, was conducted in Germany, Austria, the United States, and the United Kingdom. The study enrolled 25 children aged 2 to 7 years with a family history of T1D and who were islet autoantibodies–negative. The children were randomized to receive either oral insulin or placebo once daily. The study results showed there was an immune response without hypoglycemia at high doses; however, there were almost twice as many adverse events—67 versus 35, respectively—in the insulin-treated compared with the placebo group.[3] This might be an interesting treatment option, but larger trials are necessary for further study.

"Currently, there are multiple ongoing studies and over 150,000 patients have been screened to determine predisposition of developing T1D," said Insel. JDRF is funding multiple trials along with National Institutes of Health's TrialNet trials. "Some of the trials are looking to arrest the progression to T1D." Although this is currently in the research setting, there are high expectations from the results of these studies.

SUMMARY

Postponing or preventing T1D is an exciting concept. Although extensive groundwork is necessary to identify the right precursors, determine the correct agents, and maintain optimal glucose control, the focus on this patient population will have a huge impact. Additionally, looking at adjunct therapy to help optimize insulin therapy in patients with T1D needs ongoing research. There is some excitement in the identification of the mechanism and management of T1D, which is long overdue. Ongoing trials are evaluating ways to arrest progression, perhaps using some of the

newer agents to help improve the response to insulin or to prevent the rapid breakdown of insulin. **EBDM**

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US Employee Wellness Programs and Access to Obesity Treatment in Employer-Sponsored Health Insurance

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ABSTRACT

Objectives. Under provisions of the Affordable Care Act (ACA), employers may impose substantial penalties on employees who miss specific wellness goals. This study examined the prevalence of employer practices linking wellness programs, goals for weight, and other health indicators, with access to evidence-based obesity treatment.

Methods. The study utilized a representative sample of 9644 US adults designed to match US population demographics based on gender, age, and geographic location in May 2013. Respondents were asked whether their employer (1) requires participation in a wellness program to receive full health benefits, (2) sets goals for weight and other health indicators, and (3) includes coverage for evidence-based obesity treatment in their health plan. Descriptive statistics provided sample characteristics and distribution of all variables. Pearson's chi-square analyses were used to evaluate differences in the responses for each outcome, with further assessment through multivariable logistic regression models.

Results. The study found 16% of employers required participation in wellness programs to receive full health benefits. Most programs set targets for weight and related health indicators, but they did not typically provide coverage for evidence-based obesity treatments.

Conclusions. For people seriously affected by obesity, the coverage gap described here is problematic because substantial improvement in their condition is unlikely without evidence-based treatment.

Introduction

Approximately 36% of US adults are obese, defined by the CDC as having a body mass index (BMI) ≥30.[1] It is known that persons with obesity have a higher likelihood of having co-morbid conditions such as type 2 diabetes, hypertension, cardiovascular disease, and obstructive sleep apnea. In addition, persons with obesity have significantly higher health-related costs than their normal-weight counterparts.[2]

One strategy that has been entertained to reduce obesity and subsequent healthcare costs is the utilization of employer-sponsored wellness programs. More than 60% of Americans receive their health insurance through their employer.[3] Despite the recent recession and implementation of the ACA, employers will likely continue to prevail as the top provider of healthcare insurance to Americans.[4]

Employers have begun to try to manage health costs by addressing their employees' key lifestyle risk factors.[5] In 2005, physical inactivity, overweight, and obesity were associated with more than 20% of health plan healthcare charges and more than 25% of national healthcare charges.[6] Health economists have projected that the total healthcare costs attributable to obesity or overweight will double every decade to $860.7 to $956.9 billion US by 2030, accounting for 16% to 18% of total US healthcare costs.[7]

The ACA includes provisions that permit employers who implement wellness programs to impose financial penalties on employees who do not meet specific health-related goals, including BMI. Although these provisions took effect in 2014, a growing number of employers had already begun implementing programs that require employee participation as a condition for receiving more than minimal health benefits.[8] Towers Watson and the National Business Group on Health report that rewards and penalties for health outcomes such as BMI, blood pressure, and cholesterol are growing rapidly and that the proportion of employers using them will approximately double to 28% of employers in 2014 and grow to 68% in 2015.[9]

Yet, evidence of long-term effectiveness for financial penalties based on health outcomes is lacking. Horwitz and colleagues recently reviewed randomized controlled trials of workplace wellness programs and concluded that any savings to employers from these programs are likely to be the result of cost-shifting to employees with higher health risks, such as obesity.[10] Mattke and colleagues recently published a comprehensive analysis of workplace wellness programs and found low participation (10%) and minimal effects (~1 lb/year over 3 years) for interventions targeting obesity.[11]

Concerns about the potential for discrimination against people at increased risk for obesity led the US Departments of Treasury, Labor, and Health and Human Services to issue final regulations for wellness programs under the ACA that include significant protections against these programs being used as a subterfuge for discrimination.[12] For the same reasons, in 2013, the Obesity Society published a position statement recommending against financial incentives or penalties based on an employee's weight or BMI.[13] The objective of the present study was to examine the prevalence of employer practices linking wellness programs to goals for weight and

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TABLE 1. Wellness: What Employers Require

Does your employer require participation in a wellness program before you can get the maximum health benefits they offer?	Yes n (%) (n = 1005)	No/Not Employed n (%) (n = 8466)	*P*
Age			0.0022[a]
18-24	94 (11.14)	930 (13.37)	
25-34	155 (18.36)	1087 (15.63)	
35-44	164 (19.43)	1136 (16.33)	
45-54	202 (23.93)	1551 (22.30)	
55-64	148 (17.54)	1394 (20.04)	
65+	81 (9.60)	858 (12.33)	
Gender			0.0003[a]
Female	386 (44.06)	3712 (50.46)	
Male	490 (55.94)	3645 (49.54)	
Urban Density			0.0392[a]
Rural	106 (10.55)	1121 (13.24)	
Suburban	471 (46.87)	3955 (46.72)	
Urban	428 (42.59)	3390 (40.04)	
Income			0.1565
$0-$49,999	634 (61.85)	5555 (64.66)	
$50,000-$74,999	2454 (30.04)	310 (28.56)	
$75,000+	582 (7.90)	81 (6.77)	

[a]Results refer to statistically significant variables at $P < .05$.

TABLE 2. Characteristics of Those Answering "Yes"

Employer requires participation in a wellness program before you can get the maximum health benefits they offer (n = 1005)	Unadjusted		Adjusted	
	OR	CI	OR	CI
Age				
18-24	1.00	ref	1.00	ref
25-34	1.41[b]	1.08[b], 1.85[b]	1.34[b]	1.02[b], 1.76[b]
35-44	1.42[b]	1.09[b], 1.87[b]	1.38[b]	1.05[b], 1.80[b]
45-54	1.29	0.99, 1.67	1.29	0.99, 1.67
55-64	1.05	0.80, 1.38	1.07	0.81, 1.40
65+	0.93	0.68, 1.28	0.92	0.67, 1.27
Gender				
Female	1.00	ref	1.00	ref
Male	1.29[b]	1.12[b], 1.49[b]	1.24[b]	1.08[b], 1.44[b]
Urban Density				
Rural	1.00	ref	1.00	ref
Suburban	1.26[b]	1.01[b], 1.57[b]	1.10	0.87, 1.39
Urban	1.34[b]	1.07[b], 1.67[b]	1.12	0.89, 1.43
Income				
$0-$49,999	1.00	ref	1.00	ref
$50,000-$74,999	1.11	0.96, 1.56	1.10	0.94, 1.30
$75,000+	1.22	0.95, 1.56	1.17	0.88, 1.54

* This model was adjusted for all covariates such as age, gender, urban density, and income, with estimates presented in the relevant columns.
[b]Results refer to statistically significant variables relative to the reference group (REF) at P <.05. Odds Ratio refers to whether respondents with that characteristic are more likely to have an employer that requires wellness plan participation to receive full health benefits.

other health indicators and the access of employees in such programs to evidence-based obesity treatment through employer-sponsored health plans.

METHODS

Data Sources. A stratified representative sample of US adults was recruited in May 2013 for an anonymous, voluntary online survey through Google Surveys. As described by McDonald et al,[14] this methodology draws from a broader sample of Internet users and delivers a higher response rate than typical Internet panel surveys and Internet intercept surveys due to the brevity of the questions. Using inferred demographics means that respondents answer only 1 or 2 questions. In a comparison of this methodology with both probability- and nonprobability-based Internet panel surveys, the accuracy of results was found to be equivalent or superior. The research performed herein is considered Institutional Review Board-exempt, as it involves research in which persons complete a survey. The information obtained is recorded in a manner that is unidentified and may not be linked to individual survey respondents.

The general population sample of 9644 adults (POP) was constructed to match US population demographics based upon gender, age, and geographic location. Respondents were asked if their employer:

- Requires wellness plan participation to receive full health benefits
- Sets goals for weight and other health indicators
- Covers evidence-based obesity treatments

The total sample yielded 6608 employed adults (EMP) prepared to answer questions about their employer's wellness programs. Characteristics of the sample are summarized in TABLE 1.

Statistical Analysis. Descriptive statistics were used to provide sample characteristics by whether or not respondent's employer requires wellness plan participation to receive full health benefits. A $P < .05$ determined a significant association. To assess the differences in those whose employers require wellness plans, multivariable logistic regression models were conducted, adjusting for age, gender, urban density, and income. Odds ratios and 95% CIs were reported for each outcome. Frequency distributions were used to determine the prevalence of employers setting goals for health indicators and the prevalence of employers covering evidence-based obesity treatment. All missing variables were removed from this analysis. All analyses were conducted using SAS version 9.2.

RESULTS

TABLE 1 characterizes the overall sample by total survey respondents (POP) and those survey respondents who answered questions about their employer's wellness programs (EMP). TABLE 2 presents the characteristics of those who responded to the question, "Does your employer require participation in a wellness program before you can get the maximum health benefits they offer?" by age, gender, urban density, and income. Of 6608 employed adults, 16% reported that their employer required participation in a wellness program to get the maximum health benefit. Persons who reported an employer requirement were more likely to be 25-44 years old, male, and urban or suburban.

DISCUSSION

The study found that 16% of employees report that their employer requires them to participate in wellness programs to receive their full health benefits. Most

employees faced with outcome-based incentives in their employer's wellness programs report that weight is the most common target. But most of those employees report not having access to evidence-based obesity treatment in their employer's health plans.

This study has some important limitations. Drawing the sample from Internet users introduces bias because Internet penetration in America is only 78% of adults. Internet users tend to be younger, more educated, and have higher incomes. Participants are recruited from a network of content providers that is large, but cannot represent the full breadth of Internet content available. Demographic data are inferred from IP addresses and cookies. Though this method helps to improve response rates and reduce sampling error, respondents are not explicitly answering questions about demographics as they do in more traditional surveys. This can introduce errors at the level of individual respondents, even though aggregate demographic findings are generally comparable to more traditional methods.

While these results come from a national sample, they rely on the self-reported information provided by survey respondents about their employer's wellness program and coverage of health benefits related to obesity. Some survey respondents may not have been well informed about their employer's wellness program and coverage. The study might have been strengthened by querying the employers of those who responded to the survey to ascertain if the information provided by the employees was congruent.

Nonetheless, to our knowledge, this is the first study which has sought to determine whether employers who require their employees to meet health indicator goals, such as weight loss, provide coverage for their employees to achieve goals. For people seriously affected by obesity, the coverage gap described here is serious because substantial improvement in obesity is unlikely without evidence-based treatment. This is true because obesity and its complications are typically chronic and progressive.[15] Wellness programs may have little impact on costs driven by severe obesity in the absence of access to effective treatment for this chronic disease. **EBDM**

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Community as Part of the Prescription: Social Media in Diabetes Care

KERRI SPARLING; AMY TENDERICH, MA; AND HOPE WARSHAW MMSC, RD, CDE

INTRODUCTION

In April 2015, Kerri Sparling; Amy Tenderich, MA; and Hope Warshaw, MMSc, RD, CDE, participated in the panel discussion, "Community as Part of the Prescription: Social Media in Diabetes Care," during Patient-Centered Diabetes Care, a conference jointly presented by *The American Journal of Managed Care* and Joslin Diabetes Center in Boston. This article is based on the themes outlined during that session and recent research on the use of social media to improve diabetes management.

Sparling, who was diagnosed with type 1 diabetes (T1D) at age 7, is a diabetes advocate who writes the blog, Six Until Me. Tenderich was diagnosed with T1D at age 37; a technology writer, she founded DiabetesMine, which was acquired this year by San Francisco-based Healthline Networks. Both Tenderich and Sparling are listed among the top online influencers for diabetes by ShareCare.[1] Warshaw is a diabetes educator, dietitian, freelance writer, and the owner of Hope Warshaw Associates, LLC. She was an early adopter of social media and has actively supported the growth and importance of the diabetes online community (DOC) among healthcare providers.

THE IMPORTANCE OF SOCIAL MEDIA IN DIABETES CARE

The use of social media among people with diabetes, and people and professionals who support them, has experienced tremendous growth since its initiation about 10 years ago. This demonstrates the need for clinicians to encourage engagement as complementary to clinical care. People with diabetes, both T1D and type 2 diabetes (T2D), want and need practical information about living with their disease around-the-clock, 365 days a year, as well as feedback from a community of individuals who share similar experiences. Through social media, people with diabetes find their tribe, their peers, and their comrades who are all on a unique journey. Those seeking to connect have a way of finding each other—the Twitter hashtag #DOC allows anyone on Twitter to follow the tweets of the "Diabetes Online Community."[2]

Since social media emerged in 2005,[3] the number and diversity of Facebook pages, Twitter accounts, and blogs that allow 2-way interaction between the account creator and readers or followers have increased dramatically. A recent report in *Current Diabetes Review* by Hilliard et al on the evolution of the DOC, found more than 1000 Facebook groups with the word "diabetes" as of September 2014, and a weekly 1-hour Twitter forum that draws 60 to 100 participants. The report also outlined the variety of online communication venues, including social media.[2]

The "Learn, Engage, Connect" resource guide (links to the resource can be found within Warshaw's website at http://www.hopewarshaw.com/diabetes-online-community) was developed by DOC members to assist clinicians to identify

ABOUT THE AUTHORS

KERRI SPARLING

Ms Sparling is a diabetes advocate who writes the blog, Six Until Me. She was diagnosed with type 1 diabetes at age 7. She has been listed as a top online influencer for diabetes by ShareCare.

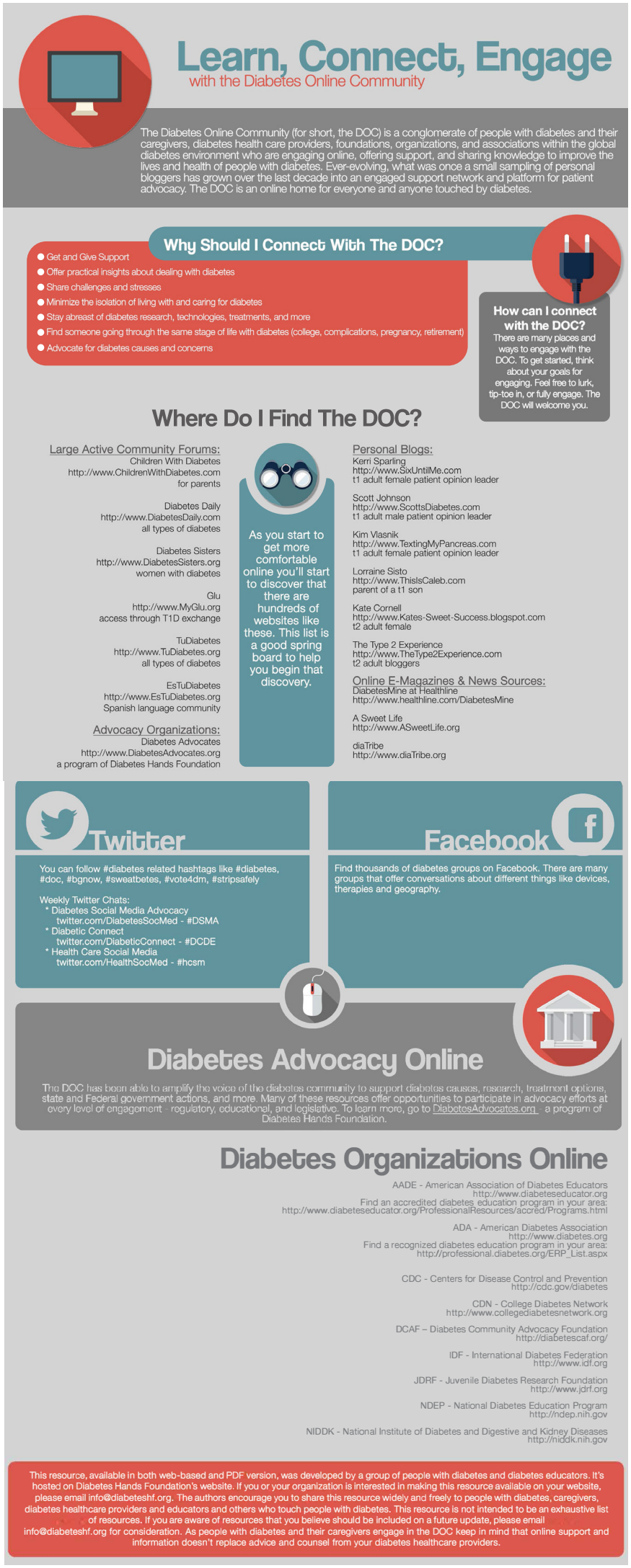
AMY TENDERICH

Ms Tenderich founded DiabetesMine after being diagnosed with type 1 diabetes at age 37. DiabetesMine was acquired this year by San Francisco-based Healthline. Ms. Tenderich has been listed as a top online influencer for diabetes by ShareCare.

HOPE WARSHAW, MMSC, RD, CDE

Ms Warshaw is a diabetes educator, dietitian, freelance writer, and the owner of Hope Warshaw Associates, LLC. She was an early adopter of social media and a supporter of the importance of the Diabetes Online Community among healthcare providers.

FIGURE. Learn, Engage, Connect can be accessed at www.hopewarshaw.com/diabetes-online-community.



and provide clients with a starter guide to websites, personal blogs, and online forums where people living with diabetes can connect with others and find reliable information.[4] Our own experience has shown that especially among people with T1D and their families, there is great desire to share: on Twitter alone, DiabetesMine has more than 25,000 followers and the Six Until Me account has more than 21,200 followers.[5,6]

Social media is not a replacement for good clinical care or working with a diabetes educator, but it is an essential parallel prescription for living well with the disease. Clinicians who do not have diabetes may not be able to answer questions about the day-to-day challenges of juggling medication, food choices, carbohydrate counts, glucose monitoring, and exercise—along with holding a job and taking care of a family. Just giving a patient a prescription for a medication and a set of instructions is not nearly enough. As the healthcare system encourages value-based care that requires "patient engagement," it is clear that this cannot be a top-down process; engagement must come from patients themselves, and social media offers those with diabetes and their caregivers a forum to foster investment in their own health.

While social media has much to offer, there are 4 core benefits for people with diabetes:

Social support. People with diabetes can get and give advice to others, avoid the isolation that can come from living with the disease, and find others experiencing similar life milestones, such as transitioning to college, moving out of their parents' home, going through pregnancy or choosing a new therapy or device. The stress of managing a chronic disease, both for the person and for spouses or family members, must be addressed; social media offers the benefits of a "support group" with greater convenience and greater reach.

Practical advice for day-to-day living. From the beginning, social media offered a forum for those with diabetes to ask questions about titrating, dosing, adverse effects of medications, and input on new devices for diabetes management, along with the myriad of practical questions to deal with diabetes, day to day.

Diabetes advocacy. The growth of the DOC supports advocacy efforts with pharmaceutical and device companies, and patient and professional organizations. This work includes efforts to give patients a stronger voice in the FDA approval process; it also includes fund-raising campaigns, such as the Big Blue Test run by the Diabetes Hands Foundation. Other examples are the call to involve people with diabetes more directly in product design, which has been championed by Tenderich at DiabetesMine[7]; and support for better diabetes care worldwide through the Spare a Rose, Save a Child campaign,[8] which Sparling initiated to aid the International Diabetes Federation's Life for a Child campaign.[9]

Patient health and safety. Clinicians are encouraged to monitor social media to support their patients and better understand their daily challenges. Increasingly, social media is being recognized as a resource for medical device manufacturers, public health officials, and regulators, especially in spotting trends that involve new medications or devices. Problems may come to light on social media before they are uncovered through traditional reporting systems. A 2014 study shows the potential for systematic monitoring of social media to act as a complement to FDA channels.[10]

COMPASSION, HUMOR, AND REALITY

Communication with peers on social media is different from the typical healthcare provider's office encounter. A "patient" in a clinical setting might not be honest about how often she is exercising, but a "person with diabetes" who goes online will find greater honesty, empathy, and even humor that might be lost on those not living with the disease. Others online understand that when it comes to "adherence" to one's diabetes regimen, people want to succeed—but sticking with regimens is difficult and doesn't necessarily produce consistent results, which can be highly frustrating.

Engaging with others online can empower those with diabetes to take better care of themselves, through the honesty, insight, and camaraderie the forums provide. A clinician's advice is important; support from others helps integrate that advice into daily life.

Those with diabetes who engage on social media understand its power, but clinicians and researchers have taken longer to acknowledge its value. Clinicians may be reluctant to direct patients to use social media for liability reasons. However, they should understand that newly-diagnosed patients (or their caregivers) are going to seek information online anyway, and it would be wise to have a list of trusted resources available. The Learn, Engage, Connect guide discussed above was created with this reality in mind.

The past 2 years have brought an increase in peer-reviewed studies and papers on social media in diabetes care. In September 2015, O'Keefe and Montori discussed the need for social media in *Diabetic Medicine:* "Clinicians interact with people living with a chronic dis-

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ease several times throughout the year either through primary care or outpatient settings. This cumulative interaction time is typically measured in hours, whereas the person's experience of the disease is continuous. Often the clinician's lens is focused on the disease-centered approach in that they are primarily concerned with the physiological markers of chronic disease (eg, HbA1C) for monitoring and treatment, rather than the patient-centered approach (eg, as patient-reported outcomes.)"[11]

While not limited to diabetes care, the July 2015 review by Patel et al, of studies involving social media in chronic disease demonstrated that 48% of the studies found social media was helpful, 45% found a neutral or undefined benefit, and 7% found harm. The authors reported that the use of Facebook or blogs appeared to offer the most support for patients managing chronic conditions.[12]

A small study reported in April 2015 in *Diabetes Care* appears to be the first trial to track the health outcomes of patients assigned to use social media compared with a control group. The study, involving 56 patients age 14 to 23 years in Macedonia, followed 29 patients given usual care and 27 treated using CareLink software from Medtronic Diabetes, which the patients uploaded at home for interventions done through Facebook and Skype. Patients were followed for 12 months. Both groups had improved glycated hemoglobin (A1C) at the end of the study period, although those who received the intervention had slightly better results. The usual care group reported going from an average A1C of 7.7% to 6.6%, and the intervention group going from 7.8% to 6.4%.[13]

Although it is significant that such a trial took place, this study is small and did not report quality-of-life measures or patient-reported outcomes that are important benefits of social media. Studies are needed to measure these elements; the researchers write, "Social media use allows patients to gain diabetes knowledge and information and interact in their daily insulin adjustments. Moreover, it could help patients cope better with their daily life. This brief trial suggests that patients prefer to communicate with their healthcare providers using social media. Facebook and Skype can improve diabetes control similar to regular clinic visits."[13]

REMOVING STIGMA, ESPECIALLY FOR TYPE 2

Despite the growth of telemedicine, patient use of online resources to obtain medical information still carries a stigma with many clinicians. There remains a "Wild West" quality to use of the Internet, and some wariness is warranted. However, rather than avoid the topic of social media, clinicians can help patients more by addressing it directly—they can advise patients on which sources are reliable and answer questions about things they have read online.

A second and more difficult stigma surrounds patients who have T2D. Although this group is significantly larger than the population with T1D, they are far less active on social media. (According to 2012 data from the American Diabetes Association, approximately 1.25 million people in the United States have T1D and about 27.8 million have T2D.)[14] Some of this lack of connection may be due to less access to technology or the older average age of the T2D population, but a more likely reason for the silence is the stigma associated with the disease. A person with T1D who shares this status will not be judged, but the reaction to a person with T2D may be, "What did you do to yourself?"

Feelings of discrimination and stress from living with the diabetes are documented. The DAWN2 study, which evaluated both people with diabetes and their family members, found that 45% of those with diabetes reported an elevated level of emotional distress specifically related to their disease and 14% had emotional well-being scores low enough to be suffering from depression. One of 5 reported discrimination from their disease and 22% of their family members believed that people with diabetes experience discrimination.[15]

Removing this stigma is key to encouraging the larger group with T2D to use social media to gain support and access to practical information, especially as the number and type of therapies proliferates. Interaction with peers decreases isolation and will help more people with T2D experience the empowerment they need to manage their disease. For those with T1D, the DOC has changed what it means to live with the disease, and it's time for many more with T2D to "find their tribe." **EBDM**

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Big Questions About Diabetes Lead to Answers From Those Who Have Lived With Disease the Longest:

An Interview with Joslin's George King, MD

ANDREW SMITH

George King, MD, devoted his professional life to unraveling the mysteries of diabetes, in large part because he wanted to figure out why several Asian populations, unique among the peoples of the world, are prone to developing the disease without first becoming obese.

Decades of research have yet to bring him closer to answering that question, but King has no regrets about his career choice. He is now a professor of medicine at Harvard University and the chief scientific officer at Joslin Diabetes Center. His long-term partnership with Lloyd Paul Aiello, MD, PhD, led directly to the anti-VEGF treatments, which inhibit vascular endothelial growth factor and can almost eliminate blindness caused by diabetic retinopathy and diabetic macular edema. Better still, King believes, another long-term project may eventually pay off with diagnostic tests that will predict which patients face the greatest risk of diabetic complications and treatments that will prevent some of those complications.

"I started off with big questions about the fundamental nature of diabetes and, thanks to the unexpected complexity of the disease, I still have most of those very same questions," said King. "On the bright side, thanks to great progress in basic science, my colleagues and I found ways using this basic information to discover some factors that may predict complications and some factors that protect against them."

It has long been apparent that some patients fare far better with diabetes than others, even after adjusting for glycated hemoglobin levels and other known risks. A patient who eats well,

(continued on **SP524**)

Jardiance®

(empagliflozin) tablets 10 mg/25 mg

JARDIANCE is an SGLT2 inhibitor for the treatment of adults with type 2 diabetes, in addition to diet and exercise

- Significant A1C reduction
- Once-daily oral dosing in the morning
- Significant weight loss demonstrated as a secondary endpoint*

* JARDIANCE is not indicated for weight loss.

INDICATION AND LIMITATION OF USE

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.

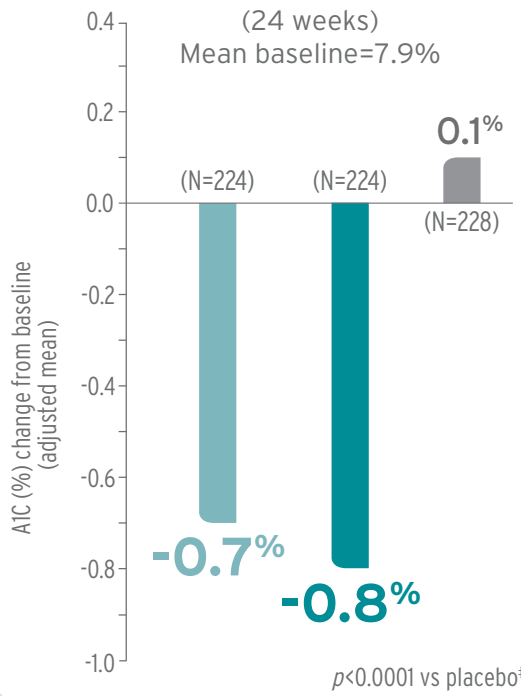
Boehringer Ingelheim

JARDIANCE is proven to significantly reduce A1C

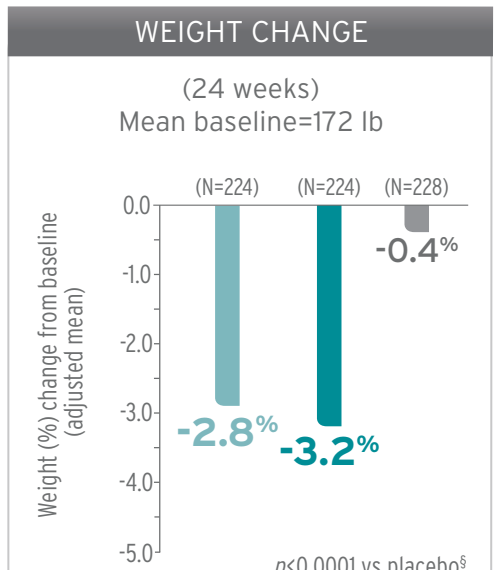
In addition to lowering A1C, JARDIANCE significantly reduced weight†

JARDIANCE monotherapy vs placebo (24 weeks)

A1C REDUCTION



WEIGHT CHANGE



JARDIANCE 10 mg ■ JARDIANCE 25 mg ■ Placebo

†JARDIANCE is not indicated for weight loss. Change from baseline in body weight was a secondary endpoint.[1]

‡A1C reduction: Difference from placebo (adjusted mean) was -0.7% and -0.9% for JARDIANCE 10 mg and 25 mg, respectively.

§Weight change: Difference from placebo (adjusted mean) was -2.5% and -2.8% for JARDIANCE 10 mg and 25 mg, respectively.

Study design: In a 24-week, double-blind, placebo-controlled study of 676 patients with type 2 diabetes mellitus, the efficacy and safety of JARDIANCE 10 mg (N=224) and 25 mg (N=224) were evaluated vs placebo (N=228). The primary endpoint was A1C change from baseline.[1]

JARDIANCE 10 mg and 25 mg significantly reduced systolic blood pressure (SBP)‖ by -2.6 mm Hg (placebo-adjusted, *p*=0.0231) and -3.4 mm Hg (placebo-corrected, *p*=0.0028), respectively, at 24 weeks[1¶]

‖JARDIANCE is not indicated as antihypertensive therapy. Change from baseline in systolic blood pressure was a secondary endpoint.[1]

¶SBP mean baseline: 133.0 mm Hg, 129.9 mm Hg, and 130.0 mm Hg for JARDIANCE 10 mg, 25 mg, and placebo, respectively.[1]

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

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Hypotension

JARDIANCE causes intravascular volume contraction. Symptomatic hypotension may occur after initiating JARDIANCE 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.

Impairment in Renal Function

JARDIANCE increases serum creatinine and decreases eGFR. Renal function should be evaluated prior to initiating JARDIANCE and periodically thereafter. More frequent monitoring is recommended with eGFR below 60 mL/min/1.73 m^2. The risk of impaired renal function with JARDIANCE is increased in elderly patients and patients with moderate renal impairment. JARDIANCE should be discontinued in patients with a persistent eGFR less than 45 mL/min/1.73 m^2.

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Learn more at www.Jardiance.com

Lilly

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Genital Mycotic Infections
JARDIANCE increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop these infections. Monitor and treat as appropriate.

Urinary Tract Infections
JARDIANCE increases the risk for urinary tract infections. Monitor and treat as appropriate.

Increased Low-Density Lipoprotein Cholesterol (LDL-C)
Increases in LDL-C can occur with JARDIANCE. Monitor and treat as appropriate.

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JARDIANCE or any other antidiabetic drug.

ADVERSE REACTIONS
The most common adverse reactions (>5%) associated with placebo and JARDIANCE 10 mg and 25 mg were urinary tract infections (7.6%, 9.3%, 7.6%, respectively) and female genital mycotic infections (1.5%, 5.4%, 6.4%, respectively).

When JARDIANCE was administered with insulin or sulfonylurea, the incidence of hypoglycemic events was increased.

DRUG INTERACTIONS
Coadministration of JARDIANCE with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.

USE IN SPECIAL POPULATIONS

Pregnancy
There are no adequate and well-controlled studies of JARDIANCE in pregnant women. JARDIANCE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known if JARDIANCE is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from JARDIANCE, discontinue nursing or discontinue JARDIANCE.

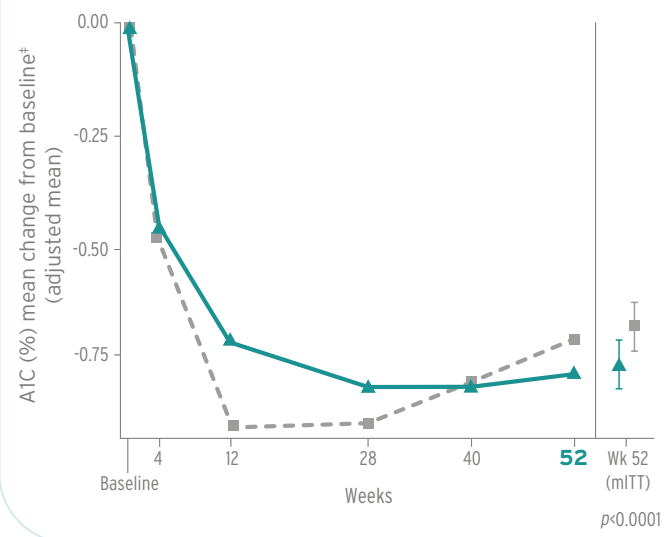
Geriatric Use
JARDIANCE is expected to have diminished efficacy in elderly patients with renal impairment. The incidence of volume depletion-related adverse reactions and urinary tract infections increased in patients ≥ 75 years treated
with JARDIANCE.

JARPROFISI 8.2.14

In adults with type 2 diabetes,

JARDIANCE demonstrated similar A1C reduction vs glimepiride with the additional benefit of significant weight loss*

A1C REDUCTION IN A 52-WEEK INTERIM ANALYSIS†

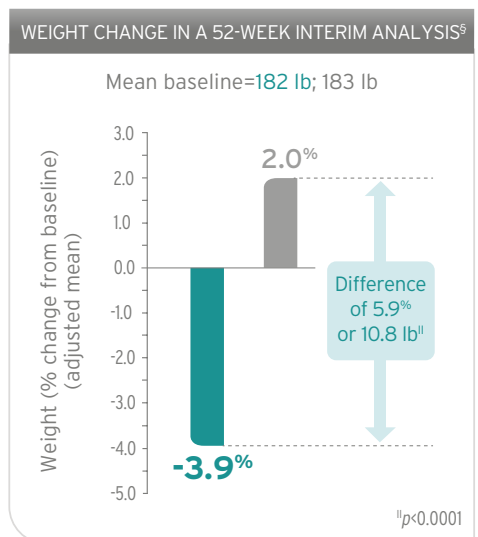


JARDIANCE 25 mg + metformin (N=693)

Glimepiride + metformin (N=700)

*JARDIANCE is not indicated for weight loss. Change from baseline in body weight was a secondary endpoint.[1]

WEIGHT CHANGE IN A 52-WEEK INTERIM ANALYSIS§



JARDIANCE 25 mg + metformin (N=765)

Glimepiride + metformin (N=780)

Study design: In a 104-week, double-blind study of 1,545 patients with type 2 diabetes mellitus, the efficacy of JARDIANCE 25 mg as add-on therapy to metformin (N=765) was evaluated vs glimepiride (mean daily dose 2.7 mg) added to metformin (N=780), administered once daily.

†Completers only.

‡Mean change from baseline adjusted for baseline A1C, geographical region, and eGFR at baseline.

§Modified intent-to-treat population (mITT). Last observation on study (LOCF) was used to impute data missing at Week 52.

#SBP mean baseline: 133.4 mm Hg and 133.5 mm Hg for JARDIANCE 25 mg and glimepiride, respectively.[1]

JARDIANCE 25 mg significantly reduced SBP¶ (-3.6 mm Hg) vs an increase with glimepiride (2.2 mm Hg) at 52 weeks; adjusted mean, $p<0.0001$#

¶JARDIANCE is not indicated as antihypertensive therapy. Change from baseline in systolic blood pressure was a secondary endpoint.[1]

- The recommended dose of JARDIANCE is 10 mg once daily. In patients tolerating JARDIANCE 10 mg, the dose may be increased to 25 mg
- Primary endpoint was A1C change from baseline after 52 weeks and 104 weeks.[1] At 52 weeks, change from baseline (adjusted mean) was -0.7% with both JARDIANCE and glimepiride. Data at 104 weeks are not yet available

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 to reduce the risk of hypoglycemia when used in combination with JARDIANCE.

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

Reference: 1. Data on file. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. 2014.

Jardiance®
(empagliflozin) tablets
10 mg/25 mg

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. **Limitation 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]*. **Impairment in Renal Function:** JARDIANCE increases serum creatinine and decreases eGFR *[see Adverse Reactions]*. The risk of impaired renal function with JARDIANCE is increased in elderly patients and patients with moderate renal impairment. More frequent monitoring of renal function is recommended in these patients *[see Use in Specific Populations]*. Renal function should be evaluated prior to initiating JARDIANCE and periodically thereafter. **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. **Urinary Tract Infections:** JARDIANCE increases the risk for urinary tract infections *[see Adverse Reactions]*. 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. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JARDIANCE or any other antidiabetic drug.

ADVERSE REACTIONS: The following important adverse reactions are described below and elsewhere in the labeling: Hypotension *[see Warnings and Precautions]*; Impairment in Renal Function *[see Warnings and Precautions]*; Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*; Genital Mycotic Infections *[see Warnings and Precautions]*; Urinary Tract 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 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. *Impairment in Renal Function:* Use of 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]*.

Table 2: Changes from Baseline in Serum Creatinine and eGFR 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
		Moderate Renal Impairment[a]		
		Placebo		JARDIANCE 25 mg
Baseline	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

[a]Subset of patients from renal impairment study with eGFR 30 to less than 60 mL/min/1.73 m^2

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 Controlled Clinical Studies

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%

Table 3 (cont'd)			
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 Insulin (18 weeks[c])	**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%

[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]Insulin dose could not be adjusted during the initial 18 week treatment period

Genital Mycotic Infections: In the pool 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 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.

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: ***Pregnancy Category C:*** There are no adequate and well-controlled studies of JARDIANCE in pregnant women. JARDIANCE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on results from animal studies, empagliflozin may affect renal development and maturation. In studies conducted in rats, empagliflozin crosses the placenta and reaches fetal tissues. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. **Nursing Mothers:** It is not known if JARDIANCE is excreted in human milk. Empagliflozin is secreted in the milk of lactating rats reaching levels up to 5 times higher than that in maternal plasma. 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 many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from JARDIANCE, a decision should be made whether to discontinue nursing or to discontinue JARDIANCE, taking into account the importance of the drug to the mother. **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. 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 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 Warning 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. 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

JAR-BS-8/14 JAR582220PROF

Boehringer Ingelheim

Lilly

(continued from **SP517**)

ABOUT THE EXPERT

GEORGE KING, MD

Dr King is the chief scientific officer at Joslin Diabetes Center and professor of medicine, Harvard University.

exercises, and controls blood sugar can lose kidney function 10 years after diagnosis and die shortly thereafter. Another patient can eat doughnuts, be on 1 or 2 insulin shots a day, and live 50 healthy years. Researchers have always looked for hidden factors that explain such differences, but King recognized years ago that an initiative begun in 1948, along with advances in information technology (IT), might allow him to make connections that others had missed.

The initiative, dubbed the Joslin Medalist Program, attempts to improve self-management among patients with type 1 diabetes (T1D) by giving medals to long-time survivors; the first medals went to people who lived with the disease for 25 years. However, survival periods grew so much with the passing of time that Joslin presented its first 80-year medal in 2013. The program effectively gave Joslin a very large list of people who fared extraordinarily well with T1D, a list that just begged to be converted into a long-term study cohort.

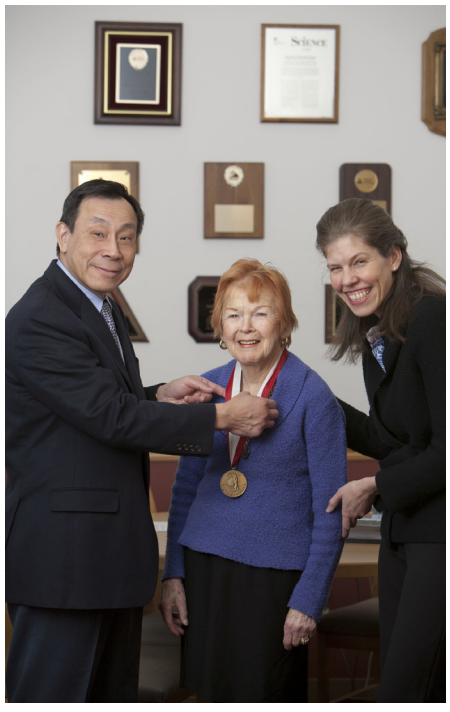
King and his team started a decade ago with about 550 people who had survived at least 50 years beyond their initial diagnosis.[1] Since then, the researchers have performed yearly physicals on each patient and taken samples of blood, urine, and DNA, with follow-up visits every 3 years. They have also tried to convince cohort members to donate their organs to Joslin.

"Large biopsies would be ideal, but patients are understandably reluctant to give us significant portions of organs they're still using, so this program has been the primary source of invaluable tissue samples," said King. "It's critical, though, that we get them as soon as possible after they die. Ideally, either the patient or a family member will contact us when death seems imminent, so we can make arrangements to preserve the tissue."

Not every patient has undergone every checkup and only about half have agreed to donate their organs, but Joslin has still collected a huge amount of biological information about how T1D affects a highly resistant population over long periods of time. In years past, this data would have overwhelmed researchers, obscuring all but the most obvious connections, but IT has made it possible to take several million data points for each patient and compare hundreds of patients in the search for patterns that explain (or at least predict) outcomes.

"Much of the value in this cohort lies in the fact that although its members have all done better than most type 1 patients, they're still a heterogeneous group. Different members eventually suffer different complications. Some have kidney problems but perfect eyes, while others have eye problems but perfect kidneys. That allows us to compare and contrast patients who do and don't suffer a particular complication," said King. "Of course, it would be impossible to separate relevant data from noise if we had just a few patients to compare, but when you have hundreds of subjects in each group, you can narrow down the possibilities enough to test them."

Once King and his team think they may have identified a protective factor against a particular complication, they move to the lab to evaluate the hypothesis. If, for example, they find a protein that may protect the eye, they will culture eye cells, overexpress the protein in some batches of eye cells, and see if the enhanced eye cells fare better than control cells when they simulate the effects of T1D, such as hyperglycemia.



George King, MD, and Hillary Keenan, PhD, co-principal investigator for the Joslin Medalist study, congratulate a 75-year medalist, Kathryn Hamm.

If a possible protective factor works in the test tube, the researchers move on to animal models. Typically, they will engineer a mouse to express the relevant factor (and to develop T1D) and then see if that factor protects mice against the associated complication. If such experiments produce positive results—and the vast majority of potential protective factors fail before this point—then Joslin looks for partners in pharmaceuticals or biotech to help translate this basic research into actual treatments.

King and his colleagues have been using this basic protocol to test potential protective factors for many years now. It has yet to produce a commercial treatment for patients with diabetes, but it has identified a number of possible drug targets. Joslin's partners are currently using animals to test compounds that bind with 1 eye-related target and 1 kidney-related target. If all goes well, King says, efforts could progress to clinical trials of entirely novel treatments in 3 to 5 years.

The predictive tools that emerge from Joslin's labs could eventually power commercial testing products, but it would take years of testing to secure regulatory approval for any such offering.

"When we first started the process, we hoped that we would find a single factor that protected against all diabetic complications. In reality, we've found different factors that seem to protect against different complications, which is logical given that different people develop different complications," King said. "On the bright side, most of the potential protective factors we have identified are proteins and metabolons, which often lend themselves to drug development, rather than bits of genetic code, which do not."

The duration of Joslin's Medalist study has also allowed King to undertake a Big Data approach to developing tests that predict which patients are likely to develop particular complications at particular times. The process starts by taking all cohort patients who developed a certain complication after they joined the study and then analyzing data collected from them before that diagnosis. If, say, there are common elements in blood tests taken from most study group members 5 years before kidney failure (elements that are rare in tests from patients whose kidneys will still be working in 5 years), software can sometimes point them out to researchers who can then test the predictive power of those biomarkers in other patients.

Of course, validating the predictive powers of biomarkers would be impractical if it had to be done in real time. Any prospective trial that would validate a diagnostic tool's ability to predict kidney failure 10 years in advance would take 10 years or longer. Fortunately, King can demonstrate the predictive power of patterns from the long-term records of the Medalist patients by showing that they could predict outcomes using long-term records of other long-term studies which have been following a group of T1D patients for many years and collecting blood and urine for over 20 to 30 years.

King and his team believe this technique has enabled them to spot a number of biomarkers that make earlier and more accurate predictions about which patients will develop different complications. Indeed, King and his Joslin colleague Hillary Keenan, PhD, filed for a patent on a test that would gauge a patient's risk for diabetic nephropathy by testing urine, blood, or kidney tissue for the profile of proteins and metaboloms and comparing the results with those from patients who lived 25 or more years without such a complication.[2] Such a test could help doctors personalize the courses of treatments for particular patients. It could also be used to help evaluate the effectiveness of treatments designed to prevent diabetic nephropathy.

The predictive tools that emerge from Joslin's labs could eventually power commercial testing products, but it would take years of testing to secure regulatory approval for any such offering. King expects to publish information about the biomarkers discovered by his team long before that, however. He hopes that caregivers can find ways to start harnessing some of their predictive power in the next few years.

If either the diagnostic tools or therapeutic treatments that emerge from the Medalist study do transform the treatment of diabetes, it would not be the first such triumph for King. That first transformational achievement came more than 20 years ago when he and Aiello hypothesized that a compound cloned by scientists at Genentech was the "Factor X" that significantly contributed to diabetic eye disease.

The VEGF molecule had all the properties that researchers expected in Factor X. It was made in the eye, its expression increased as oxygen levels declined, and it made cells in the retina grow and leak. Starting with this observation, King and Aiello led the research that proved VEGF spurred diabetic eye disease. They subsequently worked with Genentech on the creation of a VEGF inhibitor that eventually translated into a new class of drugs to prevent vision loss from diabetic reti-

nopathy that has benefited hundreds of thousands of patients worldwide.[3,4]

King naturally hopes that the targets identified through the Medalist study prove just as useful, but they're not the only project he's excited about. "We're currently working to redesign insulin such that it would lower the risk of cardiovascular disease rather than increasing the risk [in] the way current formulations are thought do in many patients," said King. "We don't know anywhere near as much as we'd like to know about the connection between diabetes and cardiovascular disease. However, we think we've made real strides toward an insulin formulation that can decrease arteriosclerosis in mice. It's a long-term project, but it's very exciting."

Looking back on his career, King says that he has always focused most of his effort on discovering the causes for different diabetic complications. When he started, there was still hope of finding a single underlying cause for all diabetic organ failure (and thus, quite possibly, a single treatment that would protect all organs). He has come to believe (like most of his colleagues) that there is no single underlying cause, that the disease may attack each organ in a different way, and that researchers like him will have to hunt them down one by one.

"Everything has proven to be more complicated than expected, which has been frustrating, but we still made real progress in the treatment of patients," said King. "Patients survive longer and enjoy higher quality of life. VEGF inhibitors alone have already saved more than 200,000 patients from losing their vision. We have also developed a set of very powerful tools that should enable continuous progress toward better treatments." **EBDM**

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STEM CELLS AND RETINOPATHY

Exploring the Use of Stem Cells in Fat to Repair Damage From Diabetic Retinopathy

MARY K. CAFFREY

Rajashekhar Gangaraju, PhD, has seen the devastating effects of diabetes firsthand. Both his father and grandfather suffered from the disease, as well as vision loss that results from long-term damage to blood vessels in the eyes.

Now an assistant professor at the University of Tennessee Health Science Center in Memphis, Gangaraju has relocated from Indiana School of Medicine—along with a $1-million grant from the National Eye Institute—to continue his quest to halt the damage that diabetes causes. His method? Repair the damage with stem cells, using a plentiful source: fat tissue.

DIABETES AND VISION LOSS

As diabetes progresses, elevated blood sugar levels damage the blood vessels that carry nutrients to the retina. As a result, the blood vessels leak and bleed and can no longer do their job. Although the body compensates by producing more blood vessels, these are poor substitutes and leak as well, and the damage perpetuates. Hemorrhaging, retinal detachment, and blindness can result.[1]

According to the CDC, the number of Americans with vision-threatening diabetic retinopathy (DR) is projected to triple between 2005 and 2050, from 1.2 million to 3.4 million, due to an aging population and the rising incidence of diabetes.[2] With the increasing number of diabetes cases around the globe, the threat of vision loss is a worldwide problem.[3]

Treatment for DR may not occur right away. Many patients may not realize that the symptoms they are experiencing are of DR; they may attribute vision problems to cataracts or aging, which are comparatively easier to address. Once the condition progresses to diabetic macular edema (DME) treatments include injections with vascular endothelial growth factor (VEGF) inhibitors, which block the protein VEGF; this prevents abnormal blood vessels from growing and leaking fluid. While these injections represent a vast improvement over earlier available treatments, they still require repeat visits over an extended period and can be expensive.[1,4] Gangaraju sought an alternative treatment that would begin earlier and have longer-lasting effects.

POTENTIAL FOR STEM CELL THERAPY

In a 2014 paper, Gangaraju outlines the possibilities that stem cell therapy could offer for patients with diabetes suffering vision loss. He explains that DR results from the loss of pericytes, the connective tissues found in the walls of small blood vessels of the eye, and discusses their role as mediators of DR and potential targets for treatment.[5]

The key to treatment, he explains in the paper, is the discovery that adipose stem cells—which are located in fat tissue—could be used as a resource for regenerating damaged blood vessels in the retina. Unlike other potential sources of stem cells, such as bone marrow, adipose tissue is easily obtained and cells derived from it can counteract what is occurring in the blood vessels of an individual with diabetes.

"We know that the stem cells are migrating toward the blood vessels and are trying to arrest the leakage. We believe this will be a therapy helpful for early stage diabetics or those who have begun to suffer the effects of diabetes and have early vision loss due to the leaking blood vessels," Gangaraju said in a statement when the grant was announced.[6]

ENSURING SAFETY FIRST

For all the promise of stem-cell therapy, Gangaraju told *Evidence-Based Diabetes Management* that he is being extraordinarily careful before he moves into his first clinical trials with humans. (Some trials for ocular conditions are already taking place in Europe and in Mexico.) As he explained, there are many questions that must be answered: Are the cells being rejected by the host? Are there any tumors? In addition, there is the key question: how long do the effects last?

That last part is important because if it turns out that stem cell repair for retinopathy offers a long-term solution, it could represent a significant advance over current treatment with VEGF inhibitors. This will require gaining a richer understanding of exactly how the stem cells are restoring vision in the eye.

"We need to answer the question, 'What is the mechanism of action?'"Gangaraju pointed out. Although he is certainly aware of treatments taking place in Mexico for DME, because the mechanism of action is not well understood, this is simply too risky. He will take his time and wants to understand the potential for stem cell therapy on the retina. "I'm a back-of-the-eyes guy," he said.

There's hope this work will lead to a preventive measure that can be used instead of waiting for vision to deteriorate. Once Gangaraju has enough information, he can present it to the National Institutes of Health and seek approval from the FDA for the first clinical trials with humans. He expects this to happen in the next 2 to 3 years. **EBDM**

ABOUT THE EXPERT

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"Artificial Pancreas" System Performs Well in Home-Based Trial, Researchers Report

MARY K. CAFFREY

An algorithm-driven "artificial pancreas" system worked safely in a 3-month trial involving adults and children with type 1 diabetes (T1D), according to results presented September 17, 2015, at the European Association for the Study of Diabetes (EASD) in Sweden.

The trial involved 33 adults and 25 children and teens; adults used the system day and night and the younger patients used it overnight. Researchers reporting simultaneously in the *New England Journal of Medicine*[1] concluded that the system, which makes use of smartphone technology and software that continuously monitors blood sugar and insulin delivery, produced better results than the current standard of sensor-aided pump therapy. The so-called "closed loop" system "improved glucose control, reduced hypoglycemia, and, in adults, resulted in a lower glycated hemoglobin level," the authors wrote.

"We found that extended use of a closed-loop system at home over a period of 12 weeks during free daily living without close supervision is feasible in adults, children, and adolescents with type 1 diabetes," the authors continued. The study was led by Hood Thabit, MD, of the University of Cambridge in England. "We did not restrict participants' dietary intake or, after the initial 2 weeks, physical activity or geographical movements. Participants were allowed to travel and to use the system when driving."

Just less than 5% of the 29 million Americans living with diabetes have T1D,[2] which occurs when the body kills cells in the pancreas that produce insulin and glucagon, regulators of blood glucose. Elevated blood glucose levels, especially for extended periods, lead to blood vessel damage in the eyes and extremities. Acute cases of low blood glucose levels can cause patients to lose consciousness or die, and poor management of the disease over time can cause blindness, kidney damage, or loss of limbs.

Management of T1D is quite time-consuming and requires daily attention to diet and exercise coupled with constant monitoring of blood sugar levels. Patients who have T1D are known to experience stress and depression from the constant vigilance required to maintain their health. For many years, researchers have pursued development of a so-called "artificial pancreas" that would free patients from the constant need to monitor blood sugar levels; this would represent not only a huge step forward in health maintenance, but also quality of life.

Results of a trial that used smartphone technology to monitor blood sugar and insulin delivery were presented in September.

The technology presented at EASD appears to be a step toward that goal: in the portion of the study involving adults, glucose levels stayed in the target range of 70 to 180 mg/dL 68% of the time when the software controlled the release compared with 57% of the time when the volunteers controlled their insulin release. The authors said that patients with the algorithm-driven technology experienced more consistent glucose control despite the "day-to-day variability in insulin requirements," adding that the new system was a step up over new technology that has reached the market in recent years. Researchers reported just 1 incident of hypoglycemia, which was attributed to a dying battery in a device.

"Systems with threshold-suspend control and predictive low-glucose suspend control may reduce the risk of hypoglycemia, but the systems are not designed to step up insulin delivery and do not address the issue of hyperglycemia," the authors wrote. "The advantage of a closed-loop system is the responsive, graduated modulation of insulin delivery, both below and above the preset pump regimen, which allows for improvements in the proportion of time spent in target glucose range and the lowering of the mean glucose level without increasing the risk of hypoglycemia."

Aaron Kowalski, vice president of research for JDRF, said the results showed the technology was "potentially transformative." JDRF has been a leading funding source for this artificial pancreas project and others, which means that multiple competitors are racing toward a commercially viable product.[3]

There had always been concerns about what happens when users of the technology "go out in the real world where you have exercise, you might be golfing all day, eating huge meals, and drinking alcohol," Kowalski said. The study presented September 17, 2015, shows that not only does the artificial pancreas technology work, but it is safer than what most patients are doing now. **EBDM**

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Medtronic Announces US Availability of MiniMed Connect Technology

MARY K. CAFFREY

Medtronic today announced that its MiniMed Connect technology, which displays diabetes data from an insulin pump and continuous glucose monitor (CGM) on a smartphone, began shipping in the United States in late September.[1] The product received FDA clearance in June and was displayed at the 75th Scientific Sessions of the American Diabetes Association in Boston.[2] MiniMed Connect is part of a wave of technology products for persons with diabetes that marry traditional medical devices with smartphone or other consumer technology, to make glucose monitoring more discreet and convenient.

Among other features, MiniMed Connect allows persons other than the patient, such as parents or spouses, to remotely monitor diabetes information through management software known as CareLink Personal. (The Dexcom G4 Platinum with Share technology offers similar capabilities.[3]) MiniMed Connect is compatible with Medtronic's MiniMed 530G and MiniMed Revel CGM systems. Right now, the related smartphone app works with iOS devices, and Medtronic is working with Samsung to develop an Android-compatible app, according to a statement from the company.

Patients can allow healthcare providers to access diabetes information through CareLink reports, which eliminates the need for patients to record blood sugars or other information between visits. "Effective management of diabetes requires an engaged team of participants, and MiniMed Connect serves to inform and involve people with diabetes, their loved ones and their healthcare professionals," Annette Bruls, Medtronic president of Diabetes Services and Solutions, said in a statement.[1]

Rapid advances in CGM technology come as pressure grows for Medicare to cover it, as most commercial insurers do. There is concern among patient advocacy groups that Medicare's failure to cover CGM thus far, even though it has become the standard of care in type 1 diabetes, could mean the nation's largest payer would not cover artificial pancreas technology, which is on the horizon. Already, technologies that have been labeled "artificial pancreas" are announcing results of at-home trials. **EBDM**

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New Drug Application for Lixisenatide Accepted; CV Results Already in Hand

MARY K. CAFFREY

FDA has accepted a new drug application (NDA) for Sanofi's lixisenatide, a GLP-1 receptor agonist, marking the first time that such a filing included data from a cardiovascular (CV) outcomes trial, the company announced September 29, 2015.

Lixisenatide, approved in Europe under the brand name Lyxumia, treats adults with type 2 diabetes; it has been studied both alone and in combination with Sanofi's mainstay insulin, Lantus. The NDA announcement is based on results from the GetGoal clinical program, whose results were reported in 2014,[1,2] and whose CV results were presented in June at the 75th Scientific Sessions of the American Diabetes Association (ADA).[3]

In support of the NDA, Sanofi included results of 11 multinational, phase 3 clinical trials, in which the main efficacy endpoints were met, with reductions in glycated hemoglobin (A1C) ranging from 0.7% to 1.0%.[1] Results from one of those trials, reported in *Diabetic Medicine* in February 2014, found that lixisenatide, given once daily in both 1- and 2-step dose increases, significantly improved A1C at week 24 compared with placebo and allowed more patients to achieve an A1C of less than 7.0%.[2]

What sets lixisenatide apart is the ELIXA trial, which were the first CV results from the glucagon-like peptide 1 (GLP-1) receptor agonist class.[3] The trial found that there were no CV benefits or risks from the therapy, which works in the pancreas by suppressing glucagon secretion from the alpha cells and stimulating glucose-dependent insulin by the beta cells. Of note, the ELIXA trial found no risk of pancreatic injury, something that has been of particular concern to FDA.

US regulators have been requiring long-term CV trials for new diabetes and cholesterol medications in the wake of embarrassing events in the prior decade. In one episode, the agency was forced to limit sales of rosiglitazone after that blockbuster drug was linked to risk of heart attacks based on a report published in the *New England Journal of Medicine*.[4] For example, when the FDA recently approved the new class of cholesterol medications, the PCSK9 inhibitors, it limited indications while awaiting results of long-term safety trials, which are expected in 2017. Indications in Europe for these same drugs are much broader.[5]

In a statement, Sanofi's Pierre Chancel, senior vice president and head of Global Diabetes, said, "Sanofi's integrated portfolio of marketed products provides treatment, monitoring and support at every stage of the diabetes journey. Lixisenatide is a critical element of this portfolio, and we look forward to working with the FDA during the review process with the goal of bringing lixisenatide to patients in the United States."[1] **EBDM**

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Medical Device Lobbyist Stephen Ubl Named PhRMA President, CEO

LAURA JOSZT

The pharmaceutical industry's largest trade group, Pharmaceutical Research and Manufacturers of America (PhRMA), has announced that Stephen J. Ubl will be the next president and CEO.

Current president and CEO John J. Castellani announced earlier this year that he would be retiring at the end of this year. Ubl spent the last 10 years as the president and CEO of the Advanced Medical Technology Association (AdvaMed), the world's largest medical technology association.

STEPHEN J. UBL, PRESIDENT AND CEO

"Steve's extensive experience, depth of knowledge and patient-centered approach to advocacy will serve him well in leading the association at a time when our industry is bringing tremendous medical innovation to patients, the health care system and society," Kenneth C. Frazier, chairman and CEO of Merck & Co. Inc, and chairman of the PhRMA board of directors, said in a statement on September 25, 2015.[1]

As the head of AdvaMed, Ubl has a track record of working with a broad array of healthcare stakeholders and he was in charge during a period of improved relations between the FDA and the device industry. As president and CEO, he pushed for faster approval times and lobbied to repeal the Affordable Care Act's 2.3% medical device excise tax. Ubl has also been a board member of the National Health Council and he has appeared on *Modern Healthcare*'s list of 100 Most Influential People in Healthcare.

"This is an exciting time to be joining the biopharmaceutical industry as new medicines are coming to the market that are completely transforming care for patients fighting cancer, heart disease, hepatitis C and other debilitating diseases," Ubl. "I look forward to working with PhRMA member companies and the broader health care advocacy community to advance public policies that will improve patients' access to medicines and foster the continued development of new treatments and cures for patients."

Ubl's appointment follows the heels of other changes in leadership in a new era of health reform. For instance, in July, America's Health Insurance Plans named Marilyn B. Tavenner, the former CMS administrator who oversaw the troubled launch of HealthCare.gov, as the new president and CEO.[2] **EBDM**

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Type 2 Diabetes Patients Should Be Screened for Liver Disease, Study Suggests

MARY K. CAFFREY

Health plans looking to hold down the cost of complications for patients with type 2 diabetes (T2D) may want to screen for biomarkers associated with liver disease, according to study results published in the September issue of *Alimentary Pharmacology and Therapeutics*. According to the researchers, these screenings involve 2 noninvasive tests that can be done in a primary care setting.

Researchers screened 100 patients with T2D who did not have any form of liver disease. Each patient underwent magnetic resonance imaging (MRI) with hepatic protein density fat fraction, as well as magnetic resonance elastography (MRE). The patients' mean age was 59.7 years and mean body mass index (BMI) was 30.8 kg/m^2.

Screening found that nonalcoholic fatty liver disease was present in 65% of the patients screened through the MRI method, while the prevalence of advanced fibrosis was 7.1% through the MRE. Patients with nonalcoholic fatty liver disease were younger, with a higher mean BMI and waist circumference, and they were more likely to have metabolic syndrome (84.6% compared with 40% of patients without nonalcoholic fatty liver disease). Only 26% of those with nonalcoholic fatty liver disease had elevated fatty alanine amino transferase.

"This is the first prospective study that assessed the feasibility of screening for both (nonalcoholic fatty liver disease) and advanced fibrosis in type 2 diabetic patients in a primary care setting by using 2 accurate, precise, validated noninvasive image-based biomarkers," the researchers wrote. "The study cohort included a diverse population of patients with T2D that has been managed and followed by primary care providers, and was conducted in the population likely to benefit from such screening program."

The researchers recommended validating their findings in a larger study before adding these screenings to the standard of care for T2D patients in a primary care setting. **EBDM**

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Express Scripts Will Cover Both PCSK9 Inhibitors

MARY K. CAFFREY

Express Scripts, the nation's largest pharmacy benefit manager (PBM), announced October 6, 2015, that it will cover both versions of a new class of cholesterol-lowering drugs approved this summer. Coverage began on October 12, 2015.[1]

Adding the 2 PCSK9 inhibitors, alirocumab (Praluent)[2] and evolocumab (Repatha)[3] comes amid concern about the drugs' high cost and calls for the American Heart Association and American College of Cardiology to update clinical guidelines to reflect their presence in the market.[4]

Without those updates, PBMs are taking on the gatekeeper role themselves, and both Express Scripts and CVS Health had said in August they would not automatically add the new class to the national preferred formulary until they had reviewed the FDA label and negotiated discounts over the announced wholesale prices. Sanofi-Regeneron set a price of $14,600 a year for Praluent when it was approved July 24, 2015, and Amgen followed with a price of $14,100 for Repatha after its August 27, 2015, approval.[5]

Express Scripts announced it had achieved steep discounts as well as protections against future price increases for both drugs. Whereas it declined to announce discount levels, it expects to spend $750 million for the 2 drugs in 2016. That amount is well below earlier forecasts but still puts the drug class among the most costly in the market.[1,5]

STEVE MILLER, MD

"Aligned with our clients, we have achieved a more balanced marketplace, which has led to more collaborative discussions with manufacturers like Amgen, Regeneron, and Sanofi who share our interest in delivering innovative treatments to patients when clinically appropriate," said Steve Miller, MD, Express Scripts' chief medical officer. "As a result, we are confident that we have received the best price possible for both products, without having to exclude either."[1]

Having 2 drugs hit the market at once no doubt helped negotiations, and the expected arrival of more entrants into this class will create more opportunities for price controls. Pfizer's entrant could receive approval by next summer.[6]

At the same time, both drugs are in the midst of long-term cardiovascular outcomes trials that could lead to expanded FDA labels. In the United States, the drugs are only indicated for those patients at highest risk for heart disease who have been unable to control cholesterol on maximally tolerated statins. (They will also be indicated for the much smaller group of patients with familial hypercholesterolemia.) In Europe, both drugs won broader approval for patients who are statin intolerant, which will dramatically widen the pool of patients who may try them.[2,3]

Express Scripts pointed out that the new class of biologics, which require injection every 2 weeks, may be unfamiliar to patients accustomed to taking a pill every day, and special education, training, and monitoring will be required.[1]

Both drugs inhibit the proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme that when blocked, results in dramatically lower levels of low-density lipoprotein (LDL) cholesterol. PCSK9 stymies the liver from effectively eliminating LDL cholesterol on its own. When it was found that persons who lacked this enzyme had abnormally low cholesterol levels, researchers immediately recognized the therapeutic potential and began looking for ways to block PCSK9. Drugs in the class can reduce cholesterol levels up to 60%.

The total market for the 2 drugs, based on the FDA approval, has been estimated between 5 million and 10 million patients.[7] **EBDM**

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Medical World News®

POLICY UPDATE

Two Studies Say Low-Fat Diets Don't Work, Amid Wrangling Over Dietary Guidelines

MARY K. CAFFREY

Two meta-analyses of diet studies published within 8 days of each other this fall found that low-fat diets produced less weight loss than those low in carbohydrates. However, interpretations of the analyses differed, offering alternate views on how the results should affect the forthcoming *Dietary Guidelines for Americans*.

One analysis, appearing October 29, 2015 in *Lancet Diabetes & Endocrinology*[1] involved 53 studies and more than 68,000 patients, and specifically only included studies of a year or more. Sponsored by the National Institutes of Health (NIH) and the American Diabetes Association, it was accompanied by an editorial, which said that low-fat diets produced less weight loss than low-carbohydrate diets, but neither worked especially well.[2] More research was needed, the author wrote, to find out what it would take for Americans to stick with healthy eating plans.

The 2015 Dietary Guidelines Advisory Committee called for lifting the longtime limit on cholesterol as a "nutrient of concern," (top) but did say that Americans should eat less red and processed meat, such as bacon (bottom). The report also called for limits on saturated fats.

"Participants prescribed low-carbohydrate diets lost only about 1 kg of additional weight after 1 year compared with those advised to consume low-fat diets," wrote Kevin D. Hall, PhD, of the National Institute of Diabetes and Digestive and Kidney Diseases, in the editorial. (NIDDK is part of the NIH.) "Although statistically significant, such a miniscule difference in weight loss is clinically meaningless."[2]

By contrast, a meta-analysis published in *PLoSONE* October 21, 2015,[3] and sponsored by Atkins Nutritionals, was rolled out with a panel discussion at the Four Seasons Hotel in New York City, and a press release with clear conclusions: Low carbohydrate eating deserved equal billing in the nation's dietary guidelines, even though one of the panelists that day called the exercise a "fool's errand."[3,4] The panelists that day were advocates of low carbohydrate eating, led by a celebrity moderator, CNN host Lisa Ling.[4] The findings, involving 17 trials and 1797 patients, found that low carbohydrate diets produced overall weight loss of an extra 2.0 kg on average along with improved health risks.[3]

Studies, competing press releases, and hearings before Congress have been the order of the day in the weeks leading up to the release of the 2015 guidelines, which always attract intense interest. But some say this go-around has been especially hard fought, ever since the Dietary Guidelines Advisory Committee released its recommendations in February.

One of the invited guests at the Four Seasons event was Nina Teicholz, author of *The Big Fat Surprise,* whose critique of the report from the 2015 DGAC report in *BMJ* became the seminal event in the effort to upend the guidelines.

The *BMJ* article, which was picked up in some media outlets and blasted in others (BMJ issued a clarification)[5] hit just ahead of an October 7, 2015, hearing before Congress with Secretaries Tom Vilsack of the Department of Agriculture (USDA), and Sylvia Mathews Burwell of HHS, who oversee the process. A day prior, Vilsack and Burwell announced they would abandon the panel's recommendation that the 2015 guidelines take sustainability of the food supply into account.[6]

The big concern of the beef industry has been DGAC's recommendation that Americans limit consumption of red and processed meat. Lean meat, however, was considered part of a healthy diet, and the panel lifted the longtime recommendation against cholesterol for most people (those whose health conditions require limitations should follow their doctor's advice). Critics say that despite these changes and more focus on plant-based foods, there is still too much emphasis on carbohydrates. Thus, the DGAC report is also being blasted by the Sugar Association over a separate recommendation for daily added sugar limits.[4]

That's not to say that the *Dietary Guidelines* have not had flaws over the decades. In an interview with *Evidence-Based Diabetes Management*, Osama Hamdy, MD, PhD, of the Joslin Diabetes Center, said the old food pyramid that once dominated nutritional thinking did a lot of damage. But Hamdy said de-emphasizing carbs doesn't mean a diet with lots of bacon or saturated fats is a great idea, either. The Why WAIT diet he developed for a weight-loss intervention limited saturated fat to 10% of the diet and carbohydrates to 40%.[7]

In 2011, nutrition policy made a significant change at the consumer level with "My Plate," which puts less emphasis on carbohydrates; recommendations that had emphasized multiple servings of breads and cereals now said "make half your plate fruits and vegetables." On a parallel track, the FDA has been moving toward new food labels that do more to highlight added sugars, in response to criticisms that Americans backfilled fats with sugar to replace the calories.[8] **EBDM**

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Can SGLT2 Inhibitors Offer Options for Type 1 Treatment?
(CONTINUED FROM COVER)

ABOUT THE EXPERTS

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tions in blood sugar levels.

Early phase trials indicate that SGLT2 inhibitors perform both these functions in patients with T1D, but there is little evidence, to date, that such effects improve long-term outcomes. Obesity has not been common in the T1D population for long,[6] so there is no proof that obese patients fare worse in the long run than thinner patients. As for the benefits of glycemic stability, patients have long reported that dramatic changes in blood sugar make them feel lousy, but the first decent evidence to date comes from a 2015 paper that found dramatic cardiovascular benefits in SGLT2 inhibitor users. Alas, that study only looked at patients with T2D.

"Right now, the support for using SGLT2 inhibitors in T1D patients is weak. The trials that have been published, so far, demonstrate short-term safety and show us that these medications affect various biomarkers in ways that could produce long-term health benefits. The phase 3 trials are just getting under way, though, so we won't have anything resembling long-term data on large numbers of patients for some time yet. As is true for all regulatory studies, the 'long-term' trial duration is 6 to 12 months using weight and A1C as end points, as opposed to actual microvascular or macrovascular outcomes," said Irl B. Hirsch, MD, professor of medicine at the University of Washington.

"All that noted, I'm optimistic about the potential impact of SGLT2 inhibitors in T1D treatment, as are other researchers. The dangers of obesity have been so well established in virtually every population, that it's hard to believe obese type 1 patients (now a common phenotype) would not benefit from treatment that kept them 10 pounds lighter than they'd otherwise be for decades on end. It's also getting harder to believe that the abnormal rise and fall of blood sugar in type 1 patients, even those patients with low A1C levels, plays no part in their complications. Although to date we don't have definitive data on the glucose variability hypothesis, it's logical to think that SGLT2 inhibitors will help, which is why it's important to have trials and also why it's important to have randomized double-blinded trials that don't let such preconceptions obscure the truth."

There is, of course, significant evidence that moderate weight loss considerably improves outcomes among obese people in all populations, but the most concrete and compelling reason for optimism about the use of SGLT2 inhibitors in patients with T1D may come from an article that was published just this September in the *New England Journal of Medicine*.[7]

Some 7020 patients with previous cardiovascular disease were randomized among empagliflozin 10 mg, empagliflozin 25 mg, and placebo and then followed for a mean period of 3.1 years, while investigators tallied deaths from cardiovascular causes, nonfatal myocardial infarctions, and nonfatal strokes. At least 1 such event occurred in 490 (10.5%) of 4687 patients in the pooled empagliflozin group, and in 282 (12.1%) of the 2333 patients in the placebo group.

Analysis of the relative hazard ratio (HR) of empagliflozin users to placebo users found an effect that just barely reached significance (HR, 0.86; 95% CI, 0.74-0.99; $P = .04$ for superiority). Indeed, there were no significant differences between the rates of myocardial infarction or stroke. Further analysis, however, found that empagliflozin use was significantly associated with a lower risk of death from cardiovascular causes (3.7% vs 5.9%; relative risk reduction [RR], 38%), hospitalization for heart failure (2.7% vs 4.1%; relative RR, 35%), and death from any cause (5.7% vs 8.3%; relative RR, 32%).

The investigators specifically noted that such results cannot be assumed in other T2D populations with differing characteristics (let alone T1D patients, who were not mentioned at all). They also noted that the trial was designed to find effects rather than explain their causes.

"The mechanisms behind the observed benefits are speculative," the authors of the paper wrote. "We infer that the mechanisms behind the cardiovascular benefits of empagliflozin are multidimensional and possibly involve changes in arterial stiffness, cardiac function, and cardiac oxygen demand (in the absence of sympathetic-nerve activation), as well as cardiorenal effects, reduction in albuminuria, reduction in uric acid, and established effects on hyperglycemia, weight, visceral adiposity, and blood pressure."

The figures from the trial were immediately hailed as "a landmark result," by Steven E. Nissen, MD, the chairman of cardiovascular medicine at the Cleveland Clinic, and the architect of the trial design that's currently used to test the cardiovascular impact of all new medications for diabetes. Better still, officials from Johnson & Johnson announced that they expect similar cardiovascular trial results from their drug canagliflozin, and all other drugs in the class.[8]

The question, of course, is whether SGLT2 inhibitors will produce similar effects in T1D patients or even any subgroup of T1D patients. While a large and lengthy trial could answer that question with any degree of certainty, results from trials published so far suggest that SGLT2 inhibitors have similar basic effects in patients with both T1D and T2D.

A phase 2a trial of dapagliflozin,[9] for example, randomly assigned 70 adults with T1D to 2 weeks of placebo or 1 of 4 doses of the once-daily pill: 1 mg, 2.5 mg, 5 mg, or 10 mg. At the end of the study period, investigators noted that pharmacokinetic parameters were similar to those observed in patients with T2D. Glucosuria rose 88 grams per day (95% CI, 55 to 121 g/d) with dapagliflozin 10 mg, and fell by 21.5 grams per day (95% CI, –53.9 to 11.0 g/d) with placebo.

A week into the trial period, users of dapagliflozin 10 mg saw the following changes: 24-hour average blood glucose, –2.29 mmol/L (95% CI, –3.71 to –0.87); mean amplitude of glycemic excursions, –3.77 mmol/L (95% CI, –6.09 to –1.45); mean change in total daily insulin use, –16.2% (95% CI, –29.4% to –0.5%). Placebo users, on the other hand, saw smaller changes: 24-hour blood glucose, –1.13 mmol/L (95% CI, –3.63 to 1.37); mean amplitude of glycemic excursions, –0.45 mmol/L (95% CI, –4.98 to 4.08); mean change in daily insulin use, 1.7% (95% CI, –22.8% to 33.9%), respectively. These differences did not reach the level of significance, as measured by the 95% confidence intervals, but, as the investigators noted, they were about what you would see in T2D patients after the same period of time.

There were no signs of weight loss or blood pressure reduction among either dapagliflozin or placebo users during the 2-week trial, but patients from both groups (unlike their counterparts in almost any T2D trial) began the trial with healthy blood pressure measurements and body mass indexes. As for adverse events, there were no significant differences in hypoglycemia among the various groups, nor were there incidents of the adverse events that are most associated with the use of SGLT2 inhibitors: infections of the urinary tract and genitals. Such infections are probably unavoidable in the long run because all the medications in the class reduce A1C levels by reducing the amount of glucose that enters the blood via SGLT2 in the proximal renal tubules. This, in turn, increases the amount of glucose excreted via urine as well as the total amount of urine that users excrete. SGLT2 inhibitors thus have a diuretic effect and leave some patients prone to infection. (They also increase the frequency with which patients must urinate, so they should be taken in the morning rather than before bed.)[10]

Indeed, investigators did find an elevated risk of infection when they conducted a phase 2 study that randomized 300 patients among 18 weeks of canagliflozin 100 mg, canagliflozin 300 mg, or placebo.[11] They also saw the weight loss and A1C reductions that SGLT2 inhibitors produce in T2D patients. Mean weight changes were -4.2 kg (-5.1% of baseline weight) for canagliflozin 300mg users, -2.6 kg (-3.1%) for canagliflozin 100mg users, and +0.2 kg (+0.3%) for placebo users. Mean change in A1C levels was -0.24 percentage points among canagliflozin 300mg users, -0.27 percentage points among canagliflozin 100mg users, and +0.01 percentage points among placebo users. The percentage of users who achieved both end points of the trial—an A1C reduction of at least 0.4 percentage points *and* no weight gain—was 41.4 in the canagliflozin 300mg groups, 36.9 in the canagliflozin 100mg group, and 14.5 in the placebo group. Nevertheless, canagliflozin use was not associated with any increase in hypoglycemia.

Results have been similar in trials of empagliflozin.[12,13] A third trial, moreover, measured the ability of empagliflozin to affect arterial stiffness and heart rate variability (HRV) in patients with T1D and found positive effects.[14] Investigators measured HRV and circulating adrenergic mediators during clamped euglycemia (blood glucose 4 to 6 mmol/L), and hyperglycemia (blood glucose 9 to 11 mmol/L) in 40 normotensive T1D patients. They then treated the patients with 8 weeks of empagliflozin and took the measurements again.

The euglycemia measurements showed declines in systolic blood pressure (111 ± 9 to 109 ± 9 mm Hg, $P = .02$) and augmentation indices at the radial (–52% ± 16 to –57% ± 17, $P = .0001$), carotid (+1.3 ± 17.0% to –5.7 ± 17.0%, $P < .0001$) and aortic positions (+0.1 ± 13.4% to –6.2 ± 14.3%, $P < 0.0001$). The hyperglycemia measurements showed no changes in blood pressure but similar effects on arterial stiffness.

"At the very least, the results we've seen so far indicate that SGLT2 inhibitors may prove to be another tool for doing the same sorts of things to reduce blood glucose that insulin does, but in a completely unique manner. And that alone would be a valuable addition because we need more tools in this fight against diabetes. Most people with type 1 diabetes do not have the condition under good control," said Robert Henry, MD, the lead author of both the canagliflozin and dapagliflozin studies and the head of both the Center for Metabolic Research and the Section of Endocrinology, Metabolism & Diabetes at the Veterans Affairs Healthcare System of San Diego.

"If all goes well in clinical trials, SGLT2 inhibitors may prove to add considerable advantages to the management of type I diabetes—and not only for the growing number of type 1 patients who suffer from obesity and high blood pressure. Even patients who consistently keep their A1C levels below 7% may show greater glycemic variability throughout the day than people who don't have diabetes. SGLT2 inhibitors smooth out similar highs and lows in type 2 patients. They make mountains into hills and valleys into ditches and they seem to do much the same thing in type 1 patients. They also bring many other biomarkers and metabolic measurements that are unaffected by insulin closer to normal, and there is real hope their mechanism of action will benefit patients significantly more than you'd expect solely from their effect on A1C."

> **"Even patients who consistently keep their A1C levels below 7% experience far greater glycemic variability throughout the day than people who don't have diabetes. SGLT2 inhibitors smooth out similar highs and lows in type 2 patients. They make mountains into hills and valleys into ditches, and they seem to do the same thing in type 1 patients."**
>
> ROBERT HENRY, MD

Companies that develop SGLT2 inhibitors certainly seem to have real hope of receiving approval for the treatment of T1D patients. Bristol-Myers Squibb and AstraZeneca are currently recruiting for a phase 3 study of dapagliflozin in T1D patients.[15] Lilly and Boehringer, meanwhile, are recruiting for a similar study of empagliflozin.[16] (The database at ClinicalTrials.gov did not show any comparable study for canagliflozin.)

None of the companies involved would provide researchers to comment on the phase 3 trials or their expectations for SGLT2 inhibitors in T1D patients. The lead academic investigators also declined comment. **EBDM**

Mount Sinai Study Uses Big Data to Classify Type 2 Diabetes Patients Into Distinct Groups

MARY K. CAFFREY

Type 2 diabetes (T2D) behaves differently from patient to patient. But now, a team of researchers from the Icahn School of Medicine at Mount Sinai Hospital in New York has brought more clarity to this concept, with data that show T2D patients fall into 3 distinct groups.

The study, appearing in *Science Translational Medicine*, embraces the goals of President Obama's precision medicine initiative by assembling data from electronic medical records (EMR) and genotype data from 2500 people with T2D who were treated at Mount Sinai.

All patients with T2D have diminished ability to use insulin efficiently, or no ability at all. This occurs for a variety of reasons, is associated with obesity and lack of exercise. While the risk of developing T2D increases with age, more young people are being diagnosed. Some patients are more likely than others to develop disabling complications. Understanding which ones face the greatest risk could help physicians target these patients for closer monitoring and intervention.

By evaluating both the genetic information, health status, and other data points, the researchers were able to link patients to other similar patients, and eventually put patients into clusters. As this process progressed, 3 distinct subtypes emerged. According to the abstract, the Mount Sinai team identified more than 300 single nucleotide polymorphisms that were specific to each subtype. The 3 groups were:

- Subtype 1 patients were younger, with higher risk of obesity, kidney disease, and retina problems that can progress to blindness. This group had lower white blood cell counts.
- Subtype 2 patients had lower body mass index (BMI) than the group overall, but more risk of developing cancer or heart disease.
- Subtype 3 patients had a high risk of heart disease as well, but also a high risk of mental illness and allergies.

The researchers called for more work with larger groups of patients to confirm their findings–and to figure out why these subtypes form.

"These distinctions might call for tailored treatment regimens rather than a one-size-fits-all approach for T2D," the authors wrote. "Although a larger sample size is needed to determine causal relationships, this study demonstrates the potential of precision medicine." **EBDM**

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Could Patiromer Change the Face of Treatment for Patients With Diabetic Renal Disease?
(CONTINUED FROM COVER)

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cardiac output, and glycemic levels. One of the problems when managing these disease states are adverse events caused by the medications that help keep both the kidneys and heart healthy and under less stress.

Hyperkalemia is a condition that is more common in patients who have kidney disease or heart disease, and it is confounded when diabetes becomes a part of the mix. Hyperkalemia is defined as an increase in serum potassium levels in the blood—a very serious, life-threatening complication. Normal potassium levels in a healthy adult range from 3.5 mmol/L to 5.0 mmol/L. Serious increase in potassium levels, defined as >6.5 mmol/L, can lead to arrhythmias, cardiac arrest, and death within hours of the event. To understand more about hyperkalemia, it is important to understand the underlying pathophysiology that causes hyperkalemia.

As mentioned before, blood pressure control is extremely important in maintaining kidney and heart health. Both disease states require medication to keep blood pressure in the desired range, no greater than 140/90 mm Hg. Angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, and aldosterone receptor antagonists are all drug classes that are used in both heart failure and chronic kidney disease (CKD) to keep blood pressure under control and decrease the amount of stress placed on the heart and kidneys. All of these drug classes work on the renin-angiotensin-aldosterone (RAAS) system. In short, both angiotensin II and aldosterone play important roles in the reabsorption of sodium and chlorine, water retention, and the excretion of potassium in the kidneys. When these hormones are blocked—a function of ARBs and ACE inhibitors—the reabsorption of water and other electrolytes is reduced, which then decreases blood pressure, consequently relieving the stress on the heart and kidneys. However, a complication of inhibiting the RAAS system is an unwanted increase in serum potassium levels since potassium is no longer excreted as effectively, especially with decreased kidney function, which is common in diabetic renal disease.

It is extremely important to monitor potassium levels in patients in this demographic due to the fact that elevated potassium levels drastically increases their risk for mortality. When patients are in the later stages of kidney disease (stages 3 and 4), they are at increased risk for hyperkalemia due to the worsening of their kidney function, but also due to the medications they must take to manage their primary diseases. Although these patients must remain on inhibitors of the RAAS system in order to decrease kidney and heart complications, they also need close monitoring of their potassium levels, as they are at a higher risk for hyperkalemia. In these cases, physicians will advise patients to consume low-potassium diets, which means avoiding foods like beans, legumes, green leafy vegetables, potatoes and some dairy products. Physicians may also prescribe medications to lower serum potassium levels. For years, there has been only 1 FDA-approved medication for the indication of chronic hyperkalemia: Kayexelate (sodium polystyrene sulfonate).

Kayexelate works by binding potassium in the gut in exchange for sodium which prevents its absorption and causes potassium to be excreted in the feces. The drug is shown to be effective in CKD and heart failure patients who must remain on the medications that inhibit the RAAS system; however, a number of side effects associated with the drug have created barriers to prescribing Kayexelate. In 2011, the FDA issued a black box warning for Kayexelate, advising patients on the increased risk of developing colonic necrosis and gastrointestinal adverse events including bleeding, ischemic colitis, and possible perforation.[3] For patients who require chronic hyperkalemia management but have only one therapeutic option, this can be an issue. For patients at risk of serious side effects that can lead to mortality, there are no other options. The physician must decide between risk versus benefit and prescribe not only Kayexelate but also the medications that affect the RAAS system. Fortunately, recent research has addressed this unmet medical need, and there are new drugs on the horizon that look promising for the concurrent use of RAAS system–blocking drugs and chronic hyperkalemic management.

A therapy developed by the pharmaceutical company Relypsa, called patiromer, is an oral solution that works like Kayexelate in that it binds potassium in the gut to avoid absorption and excrete it in the feces. However, instead of the sodium/potassium exchange seen in Kayexelate, patiromer modulates calcium/potassium exchange, which is believed to reduce some of the adverse events associated with Kayexelate. The FDA approved patiromer, to be marketed as Veltassa, on October 21, 2015.[4]

Patiromer has demonstrated both efficacy and safety in preventing hyperkalemia events in patients with heart failure and kidney disease who were also on spironolactone therapy.[5] Another study evaluating the efficacy of patiromer found that 76% of patients with hyperkalemia were normalized following just 4 weeks of treatment. For all levels of severity, the mean potassium level was less than 5.5 mmol/L in just 2 days. In the same study, the incidence of recurrent hyperkalemia was significantly higher in the placebo group versus the patiromer group (60% vs 15%).[6]

With the apparent success in proving efficacy of the new drug, there is also the question of safety. The main adverse events reported regardless of dose were

Cost of Kidney Failure Next in CMS' Crosshairs With New ACO Model

MARY K. CAFFREY

Patients with kidney failure—also known as end-stage renal disease (ESRD)—are small in number but costly to treat. So CMS has made this group, about 600,000 Americans, the next target in its quest to trim the rate of hospital readmissions, according to a statement from the federal agency.[1]

In 2012, kidney failure patients requiring dialysis accounted for 1.1% of the Medicare population but 5.6% of its spending—a situation that cried out for a new payment model. More than a year ago, CMS called for applications for dialysis centers to take part in a new accountable care organization (ACO) model that organizes the many specialists, and encounters with the healthcare system these patients experience.

On October 7, 2015, CMS unveiled the model and a list of 13 dialysis centers that will participate. The model, known as Comprehensive ESRD Care or CEC, calls on the provider groups who treat kidney failure patients to share risk for their treatment, and to achieve savings through better coordinated care. It's based on successes in existing ACOs. According to CMS, "This model will encourage dialysis providers to think beyond their traditional roles in care delivery and support beneficiaries as they provide patient-centered care that will address beneficiaries' health needs in and out of the dialysis facility."

The model seeks different financial arrangements with dialysis centers based on their size; groups owning 200 or more facilities will be eligible for shared savings, but must take on shared risk. Those with fewer than 200 facilities can pursue shared savings but will not be liable for shared losses.

According to the National Kidney Foundation, diabetes is a major risk factor for kidney disease and failure. Diabetes injures the blood vessels in the kidneys; as the disease worsens, it can cause the kidneys to stop functioning properly and allow waste to build up in the blood. Kidney failure occurs in about 30% of patients with type 1 diabetes and between 10% and 40% of those with type 2 disease.[2] With more patients developing type 2 diabetes at younger ages, the likelihood has increased that more will develop kidney failure and require dialysis when they are past 65 years old.

Kidney failure is the latest target area for CMS, which faces aggressive goals to make more Medicare payments subject to value-based models. Federal officials are tracking procedures and treatment areas where the cost of care consumes a larger share of Medicare spending than the population would suggest, as well as common procedures that consume large shares of the budget. In July, for example, CMS issued a proposal to bundle payments for hip and knee replacements, which account for 400,000 procedures a year at a cost of $7 billion just for hospitalization.[3]

Managing renal risk was among the topics presented at the May meeting of the ACO and Emerging Healthcare Coalition meeting in San Diego, California. The Coalition is an initiative of *The American Journal of Managed Care* to help health systems learn more about changing payment models. **EBDM**

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worsening of CKD (9.2%), hypomagnesemia (8.6), worsening of hypertension (7.9%), constipation (4.6%), and diarrhea (2.7%). The main adverse event related to the actual drug was gastrointestinal issues, mainly constipation and diarrhea, neither of which were reasons for patients to withdrawal from the trial or discontinue therapy.[5]

This could drastically change how physicians approach the treatment of patients with CKD, heart failure, and diabetes who are at a higher risk of hyperkalemia. The FDA's approval of patiromer doubles the available options for long-term treatment of hyperkalemia. It also has the capability of decreasing cost by reducing hospitalizations and mortality due to hyperkalemia. Patiromer will allow patients to remain on important medications that keep their heart and kidneys healthy, which will prevent disease progression while decreasing their risks for hyperkalemia.

Whereas hyperkalemia is only a symptom or indication of other serious chronic conditions, it is just as important to monitor and prevent occurrence due to the severity and drastic increase in mortality risks, especially for patients who have comorbidities like kidney disease, diabetes, and heart failure. The promise of patiromer could significantly alter the treatment paradigm for these patients. They will not only remain controlled on their heart and kidney medications, but they also will have less concern about potassium levels increasing the chances or cardiac arrest or death. The result will be lower hospitalization costs and increased patient survival and health. **EBDM**

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TECHNOLOGY

Diabetes Management: An Age-Old Problem That Needs a Modern Day Solution

(CONTINUED FROM COVER)

tions, diagnostic approaches, device-drug combinations, patient communication, and self-management tools.

The elements to spark change are here now. What is needed, however, is a fundamental reshaping of how diabetes is approached both clinically and structurally, particularly the data/communications infrastructure and the basis by which products and services are paid. Diabetes care can be transformed with comprehensive and cost-effective outcomes solutions for patients, their providers, and their payers.

In short, diabetes is an age-old problem in need of modern-day solutions.

SHIFTING DIABETES MANAGEMENT FROM REACTIVE TO PROACTIVE

It's hard to imagine that a mere 20 years ago, hardly anyone had a cell phone, let alone one that ordered and paid for a latte delivered to the office. We lost touch with friends and colleagues as the years went by. If you needed a lift to the airport, you called the local taxi service. Technology has had an astonishing impact on how we live, exponentially simplifying everyday tasks.

Why not apply the concept to diabetes care? What if patients had continuous, easy access to the vital information that could help them and their doctors manage the disease more proactively? Does the technology exist or can it be built and connected to make this possible?

Together, Sanofi and Google Life Sciences (GLS) are answering the call to improve diabetes health outcomes with a recently announced collaboration to catapult diabetes management into the 21st century. The companies are exploring how to improve diabetes care by bringing together many of the previously siloed pieces of diabetes management, including data, analytics, drug delivery and sensor devices, and health indicators such as blood glucose and A1C levels, patient-reported information, and medication regimens. In doing so, diabetes management can shift from reactive to proactive, helping people living with diabetes and their healthcare professionals stay a step ahead of complications.

COMBINING MEDICINE, DEVICES, TECHNOLOGIES, AND SERVICES TO HELP IMPROVE DIABETES MANAGEMENT

One of the fundamental problems with managing diabetes is the sheer complexity of the disease and keeping track of it. Each day, multiple times a day, people may use a variety of devices to measure their blood glucose level and take medication accordingly. With multiple variables—such as nutrition, exercise, and sleep—affecting blood glucose, adjusting the amount of medication to avoid potentially dangerous consequences becomes essential.

In simple terms, the Sanofi/GLS collaboration strives to help people living with diabetes by developing better ways to manage the disease by using technology to understand the impact of all the variables. Currently, for most people managing this disease, the approach is almost entirely analog. Food intake, blood sugar levels, and medication doses are each tracked separately and with limited real-time feedback or guidance.

Together, Sanofi and GLS will work on finding better ways to collect, analyze, and process the multiple sources of information needed to better manage the disease. The collaboration aims to improve existing technology, invent new technology, and create enhanced accessand understanding of information. Importantly, all of this technology and information needs to be useful and actionable for people living with diabetes and their healthcare professionals in the real world, with improved outcomes as the end goal.

Although the collaboration is in its infancy, patient insights and unmet needs will be vital inputs in defining functionality and features of the solutions. It is important to ensure that patient perspectives are incorporated. In the past, Sanofi conducted market research to understand payer perspectives for integrated care solutions. The team will continue doing so to ensure that the solutions offer value-added support to what payers are doing today.

Sanofi has a deep history of creating important new offerings for people living with diabetes. As a global leader in diabetes care, Sanofi believes the company has an obligation and commitment to provide integrated solutions. This collaboration will leverage Sanofi's expertise in the treatment and biology of diabetes with the Google Life Sciences team leadership in technology to help ensure that new tools and technologies are useful in the real world. We want to help improve the patient experience, outcomes, and manage healthcare costs more effectively.

We believe that combining the complementary resources of Sanofi and GLS for a common ambition will positively impact disease management for people living with diabetes. Many people focused on the same problem will be able to create new, cost-effective tools and technologies that work together and work better for patients. The potential for integrated care solutions to help improve outcomes is there. With new technologies emerging to provide a more continuous and real-time view of patient health, we have an opportunity to make diabetes management simpler, more proactive and effective. **EBDM**

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