SPECIAL ISSUE: DIABETES AND CARDIOVASCULAR CARE

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ALSO IN THIS ISSUE

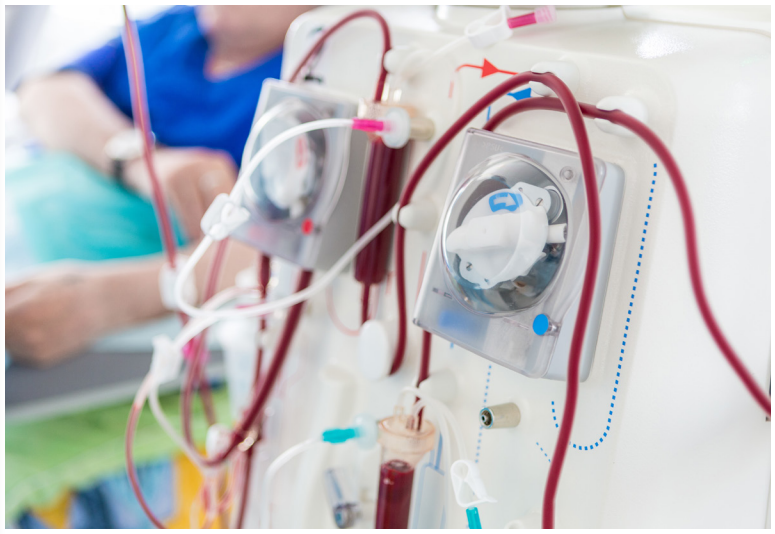
HEART FAILURE

Eldrin F. Lewis, MD, MPH, on Heart Failure's Place in Diabetes Drug Trials, and the Promise of SGLT2s in Prevention

Mary Caffrey

TEN YEARS AGO, a stunning article in the *New England Journal of Medicine* linked a blockbuster diabetes drug—rosiglitazone—with a higher risk of heart attacks.[1] The FDA soon required expansive cardiovascular (CV) outcomes trials for new glucose-lowering therapies, to make sure they did not raise the risk of heart attacks, strokes, or early death.[2]

But what about heart failure? Even though 25% of patients who develop heart failure have diabetes, and these patients tend to be far sicker and costlier to health systems,[3] the FDA's 2008 guidance focused on atherosclerotic CV disease, which occurs when plaque accumulates and hardens the arteries. Heart failure, in which the heart fails to adequately pump blood throughout the body, was not a primary endpoint in the wave of trials that followed.



End-stage renal disease is among the complications seen in patients with heart failure and diabetes.

To Eldrin F. Lewis, MD, MPH, a CV disease and transplant specialist at Brigham and Women's Hospital and an associate professor at Harvard Medical School, this was a missed opportunity. In an interview with *Evidence-Based Diabetes Management*™ (*EBDM*™), Lewis said heart failure specialists tried to sound the alarm.

"Since the FDA didn't request it, 100% of the clinical trials did not include heart failure as part of the primary composite endpoint," he said. "And for years, we in the heart failure community have been saying, 'This is a problem; this is a problem.'"

Science has brought others around, however. The first surprise came in 2013, when a safety trial found an unexpected increase in hospitalization for heart failure for the dipeptidyl peptidase-4 (DPP-4)

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PREVENTION

"Sprint to Zero": A Strategy to Address High Rates of Nontraumatic Amputations in Minority Communities

Jeffrey Carr, MD, FACC, FSCAI

EVERY DAY, APPROXIMATELY 500 Americans lose a limb and join millions of others who will struggle with a lifetime of high medical bills, disability, and significant barriers to participating in their communities.[1] The greatest risk factor for developing this condition—which is completely preventable if caught early—is diabetes, the prevalence of which is at an all-time high.[2]

Within the Medicare program, African Americans living with diabetes are nearly 3 times as likely to experience limb loss as other beneficiaries; the disparity is even worse in certain regions, such as the rural Southeast.[3] Meanwhile, Hispanics are between 50% and 75% more likely than whites to undergo an amputation,[4] and studies have shown that Native Americans—especially those living in rural Western regions—are substantially more likely to receive a diagnosis of diabetes and undergo an amputation than their white counterparts.[5]

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PAYER PERSPECTIVE

Moving Pharma Contracting Into the Era of Accountability

Thomas R. Graf, MD

WE ARE IN a unique time in healthcare. Although there are periodic crises of cost in medicine, this time we have a convergence on quality that has produced a consensus around 3 things: quality measures, the ability to measure quality in a granular fashion, and the desire for patient-oriented outcomes. This convergence has created a sharper focus on accountability for quality. Combining these new foci has resulted in a drive to improve the value proposition of medicine in America.

Currently we spend more than $3 trillion annually[1] on care that is highly variable in terms of quality,

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SP566

Blood Pressure Categories

Blood Pressure Category	Systolic mm Hg (upper #)		Diastolic mm Hg (lower #)
Normal	less than 120	and	less than 80
Elevated	120–129	and	less than 80
High Blood Pressure (Hypertension) Stage 1	130–139	or	80–89
High Blood Pressure (Hypertension) Stage 2	140 or higher	or	90 or higher

Source: American Heart Association

FEATURES

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Please see Brief Summaries of Prescribing Information on adjacent pages.

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XULTOPHY® 100/3.6 (insulin degludec and liraglutide injection), for subcutaneous use
Rx Only
BRIEF SUMMARY. Please consult package insert for full prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS: Liraglutide, one of the components of XULTOPHY® 100/3.6, causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether XULTOPHY® 100/3.6 causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions]*. XULTOPHY® 100/3.6 is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of XULTOPHY® 100/3.6 and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with XULTOPHY® 100/3.6 *[see Contraindications and Warnings and Precautions]*.

INDICATIONS AND USAGE: XULTOPHY® 100/3.6 is a combination of insulin degludec and liraglutide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily). Limitations of Use: XULTOPHY® 100/3.6 is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans *[see Warnings and Precautions]*. XULTOPHY® 100/3.6 has not been studied in patients with a history of pancreatitis *[see Warnings and Precautions]*. Consider other antidiabetic therapies in patients with a history of pancreatitis. XULTOPHY® 100/3.6 is not recommended for use in combination with any other product containing liraglutide or another GLP-1 receptor agonist *[see Warnings and Precautions]*. XULTOPHY® 100/3.6 is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. XULTOPHY® 100/3.6 has not been studied in combination with prandial insulin.

CONTRAINDICATIONS: XULTOPHY® 100/3.6 is contraindicated: In patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Warnings and Precautions]*. During episodes of hypoglycemia *[see Warnings and Precautions]*. In patients with hypersensitivity to XULTOPHY® 100/3.6, either of the active drug substances (insulin degludec or liraglutide), or any of its excipients *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors: Liraglutide, one of the components of XULTOPHY® 100/3.6, causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether XULTOPHY® 100/3.6 will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. Cases of MTC in patients treated with liraglutide have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide use in humans. XULTOPHY® 100/3.6 is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of XULTOPHY® 100/3.6 and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with XULTOPHY® 100/3.6. Such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated. **Pancreatitis:** Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with liraglutide, one of the components of XULTOPHY® 100/3.6. In clinical trials of liraglutide, there have been 13 cases of pancreatitis among liraglutide-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with liraglutide were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a liraglutide-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. After initiation of XULTOPHY® 100/3.6, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, XULTOPHY® 100/3.6 should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, restarting XULTOPHY® 100/3.6 is not recommended. Consider antidiabetic therapies other than XULTOPHY® 100/3.6 in patients with a history of pancreatitis. **Never Share a XULTOPHY® 100/3.6 Pen Between Patients:** XULTOPHY® 100/3.6 pen must never be shared between patients, even if the needle is changed. Sharing of the pen poses a risk for transmission of blood-borne pathogens. **Hyperglycemia or Hypoglycemia with Changes in XULTOPHY® 100/3.6 Regimen:** Changes in XULTOPHY® 100/3.6 regimen may affect glycemic control and predispose to hypoglycemia or hyperglycemia *[see Warnings and Precautions]*. These changes should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased. Adjustments in concomitant oral anti-diabetic treatment may be needed. When converting from basal insulin therapies or liraglutide to XULTOPHY® 100/3.6 follow dosing recommendations. **Overdose due to Medication Errors:** XULTOPHY® 100/3.6 contains two drugs: insulin degludec and liraglutide. Administration of more than 50 units of XULTOPHY® 100/3.6 daily can result in overdose of the liraglutide component. Do not exceed the 1.8 mg maximum recommended dose of liraglutide or use with other glucagon-like peptide-1 receptor agonists. Accidental mix-ups between insulin products have been reported. To avoid medication errors between XULTOPHY® 100/3.6 (an insulin containing product) and other insulin products, instruct patients to always check the label before each injection. **Hypoglycemia:** Hypoglycemia is the most common adverse reaction of insulin containing products, including XULTOPHY® 100/3.6 *[see Adverse Reactions]*. 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). XULTOPHY® 100/3.6 (an insulin-containing product) or any insulin, should not be used during episodes of hypoglycemia *[see Contraindications]*. 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]*, or in patients who experience recurrent hypoglycemia. Risk Factors for Hypoglycemia: The risk of hypoglycemia generally increases with intensity of glycemic control. The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin containing products, the glucose lowering effect time course of XULTOPHY® 100/3.6 may vary among 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. 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]*. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia *[see Use in Specific Populations]*. 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. **Acute Kidney Injury:** There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in patients treated with liraglutide, one of the components of XULTOPHY® 100/3.6 *[see Adverse Reactions]*. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide. Advise patients of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. **Hypersensitivity and Allergic Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, angioedema, bronchospasm, hypotension, and shock can occur with XULTOPHY® 100/3.6. Allergic reactions (manifested with signs and symptoms such as urticaria, rash, pruritus) have been reported with XULTOPHY® 100/3.6. There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with liraglutide, one of the components of XULTOPHY® 100/3.6 *[see Adverse Reactions]*. If a hypersensitivity reaction occurs, discontinue XULTOPHY® 100/3.6; treat per standard of care and monitor until symptoms and signs resolve. Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with XULTOPHY® 100/3.6. XULTOPHY® 100/3.6 is contraindicated in patients who have had hypersensitivity reactions to insulin degludec, liraglutide or one of the excipients of these products *[see Contraindications]*. **Hypokalemia:** All insulin-containing products, including XULTOPHY® 100/3.6, 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). **Fluid Retention and Congestive Heart Failure with Concomitant Use of a PPAR Gamma Agonist:** Peroxisome proliferator-activated receptor (PPAR)-gamma agonists can cause dose related fluid retention, particularly when used in combination with insulin containing products, including XULTOPHY® 100/3.6. Fluid retention may lead to or exacerbate congestive heart failure. Patients treated with insulin containing products, including XULTOPHY® 100/3.6 and a PPAR-gamma agonist should be observed for signs and symptoms of congestive heart failure. If congestive 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. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with XULTOPHY® 100/3.6 or any other antidiabetic drug.

ADVERSE REACTIONS: The following serious adverse reactions are described below or elsewhere in the prescribing information: Risk of Thyroid C-cell Tumors *[see Warnings and Precautions];* Pancreatitis *[see Warnings and Precautions];* Hypoglycemia *[see Warnings and Precautions];* Acute Kidney Injury *[see Warnings and Precautions];* Hypersensitivity and Allergic Reactions *[see Warnings and Precautions];* Hypokalemia *[see Warnings and Precautions]* **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 observed in practice. The data in Table 3 reflect the exposure of 1881 patients to XULTOPHY® 100/3.6 and a mean duration of exposure of 33 weeks. The mean age was 57 years and 2.8% were older than 75 years; 52.6% were male, 75.0% were White, 6.2% were Black or African American and 15.9% were Hispanic or Latino. The mean body mass index (BMI) was 31.8 kg/m^2. The mean duration of diabetes was 8.7 years and the mean HbA_{1c} at baseline was 8.2%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported in 25.4%, 12.0%, 6.5% and 6.3% respectively. The mean eGFR at baseline was 88.3 mL/min/1.73 m^2 and 6.24% of the patients had an eGFR less than 60 mL/min/1.73 m^2.

Table 3: Adverse Reactions Occurring in ≥5% of XULTOPHY® 100/3.6-Treated Patients with Type 2 Diabetes Mellitus

	XULTOPHY® 100/3.6 N = 1881 %
Nasopharyngitis	9.6
Headache	9.1
Nausea	7.8
Diarrhea	7.5
Increased Lipase	6.7
Upper respiratory tract infection	5.7

Hypoglycemia: Hypoglycemia is the most commonly observed adverse reaction in patients using insulin and insulin containing products, including XULTOPHY® 100/3.6 *[see Warnings and Precautions]*. The number of reported hypoglycemia episodes depends on the definition of hypoglycemia used, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for XULTOPHY® 100/3.6 with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that will occur in clinical practice. In the phase 3 clinical program, events of severe hypoglycemia were defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (Table 4). No clinically important differences in risk of severe hypoglycemia between XULTOPHY® 100/3.6 and comparators were observed in clinical trials.

Table 4: Severe Hypoglycemia Episodes Reported in XULTOPHY® 100/3.6-Treated Patients with T2DM

	Study A	Study B	Study C
	XULTOPHY® 100/3.6	XULTOPHY® 100/3.6	XULTOPHY® 100/3.6
Total Subjects (N)	**291**	**199**	**278**
Severe Hypoglycemia			
Percent of patients (n/total N)	0.3	0.5	0.0

Gastrointestinal Adverse Reactions: Gastrointestinal adverse reactions including nausea, diarrhea, vomiting, constipation, dyspepsia, gastritis, abdominal pain, flatulence, eructation, gastroesophageal reflux disease, abdominal distension and decreased appetite have been reported in patients treated with XULTOPHY® 100/3.6. Gastrointestinal adverse reactions may occur more frequently at the beginning of XULTOPHY® 100/3.6 therapy and diminish within a few days or weeks on continued treatment. Malignancy: *VICTOZA® (liraglutide):* In a pooled analysis of liraglutide clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for liraglutide, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events, no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among liraglutide-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established. Papillary thyroid carcinoma: *VICTOZA® (liraglutide):* In clinical trials of liraglutide, there were 7 reported cases of papillary thyroid carcinoma in patients treated with liraglutide and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound. Cholelithiasis and cholecystitis: *VICTOZA® and SAXENDA® (liraglutide):* In clinical trials of liraglutide the incidence of cholelithiasis was 0.3% in both liraglutide-treated and placebo-treated patients. The incidence of cholecystitis was 0.2% in both liraglutide treated and placebo-treated patients. In clinical trials of liraglutide at doses up to 3 mg, 1.5% and 0.6% of liraglutide-treated patients reported adverse reactions of cholelithiasis and cholecystitis versus 0.5% and 0.2% of placebo-treated patients. The majority of liraglutide-treated patients with adverse reactions of cholelithiasis and cholecystitis required cholecystectomy. Initiation of insulin containing products 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. Lipodystrophy: Long-term use of insulin containing products, including XULTOPHY® 100/3.6, can cause lipodystrophy at the site of repeated injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect absorption. Peripheral Edema: Insulin containing products, including XULTOPHY® 100/3.6, may cause sodium retention and edema, particularly if previously poor metabolic control is improved rapidly by intensified therapy. Weight Gain: Weight gain can occur with insulin containing products, including XULTOPHY® 100/3.6, and has been attributed to the anabolic effects of insulin. In study A, after 26 weeks of treatment, patients converting to XULTOPHY® 100/3.6 from liraglutide had a mean increase in body weight of 2 kg. Injection Site reactions: As with any insulin and GLP-1 receptor agonist-containing products, patients taking XULTOPHY® 100/3.6 may experience injection site reactions, including injection site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritis, warmth, and injection site mass. In the clinical program, the proportion of injection site reactions occurring in patients treated with XULTOPHY® 100/3.6 was 2.6%. These reactions were usually mild and transitory and they normally disappear during continued treatment. Systemic Allergy: Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin-containing products including XULTOPHY® 100/3.6 and may be life threatening *[see Warnings and Precautions]*. Hypersensitivity (manifested with swelling of tongue and lips, diarrhea, nausea, tiredness, and itching) and urticaria were reported. Laboratory tests: *Bilirubin: VICTOZA® (liraglutide):* In the five clinical trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of liraglutide-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown. *Calcitonin: XULTOPHY® 100/3.6:* Calcitonin, a biological marker of MTC, was measured throughout the XULTOPHY® 100/3.6 clinical development program. Among patients with pretreatment calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of XULTOPHY® 100/3.6-treated patients, 0.7% of placebo-treated patients, and 1.1% and 0.7% of active-comparator-treated patients (basal insulins and GLP-1s respectively). The clinical significance of these findings is unknown. *VICTOZA® (liraglutide):* Calcitonin, a biological marker of MTC, was measured throughout the liraglutide clinical development program. At the end of the clinical trials, adjusted mean serum calcitonin concentrations were higher in liraglutide-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. Between group differences in adjusted mean serum calcitonin values were approximately 0.1 ng/L or less. Among patients with pretreatment calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of liraglutide-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients. The clinical significance of these findings is unknown. *Lipase and Amylase: VICTOZA® (liraglutide):* In one placebo-controlled trial in renal impairment patients, a mean increase of 33% for lipase and 15% for amylase from baseline was observed for liraglutide-treated patients while placebo-treated patients had a mean decrease in lipase of 3% and a mean increase in amylase of 1%.The clinical significance of these changes is unknown. **Vital signs:** Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with XULTOPHY® 100/3.6 which is attributable to the liraglutide component. The long-term clinical effects of the increase in pulse rate have not been established *[see Warnings and Precautions]*. **Immunogenicity:** *XULTOPHY® 100/3.6:* As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

For these reasons, comparison of the incidence of antibodies to XULTOPHY® 100/3.6 in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. Administration of XULTOPHY® 100/3.6 may cause formation of antibodies against insulin degludec and/or liraglutide. In rare cases, the presence of such antibodies may necessitate adjustment of the XULTOPHY® 100/3.6 dose in order to correct a tendency to hyper- or hypoglycemia. In the clinical trials where antibodies were measured in patients receiving XULTOPHY® 100/3.6, 11.1% of patients were positive for insulin degludec specific antibodies at end of treatment vs. 2.4% at baseline, 30.8% of patients were positive for antibodies cross-reacting with human insulin at end of treatment vs. 14.6% at baseline. 2.1% of patients were positive for anti-liraglutide antibodies at end of treatment (no patients were positive at baseline). Antibody formation has not been associated with reduced efficacy of XULTOPHY® 100/3.6. *VICTOZA® (liraglutide):* Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with liraglutide may develop anti-liraglutide antibodies. Approximately 50-70% of liraglutide-treated patients in five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these liraglutide-treated patients. Sampling was not performed uniformly across all patients in the clinical trials, and this may have resulted in an underestimate of the actual percentage of patients who developed antibodies. Crossreacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the liraglutide-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the liraglutide-treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an in vitro assay occurred in 2.3% of the liraglutide-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the liraglutide-treated patients in the double-blind 26-week add-on combination therapy trials. Among liraglutide-treated patients who developed anti-liraglutide antibodies, the most common category of adverse reactions was that of infections, which occurred among 40% of these patients compared to 36%, 34% and 35% of antibody-negative liraglutide-treated, placebo-treated and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among liraglutide-treated antibody-positive patients were primarily non-serious upper respiratory tract infections, which occurred among 11% of liraglutide-treated antibody-positive patients; and among 7%, 7% and 5% of antibody-negative liraglutide-treated, placebo-treated and active-control-treated patients, respectively. Among liraglutide-treated antibody-negative patients, the most common category of adverse reactions was that of gastrointestinal events, which occurred in 43%, 18% and 19% of antibody-negative liraglutide-treated, placebo-treated and active-control-treated patients, respectively. Antibody formation was not associated with reduced efficacy of liraglutide when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with liraglutide treatment. In five double-blind clinical trials of liraglutide, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of liraglutide-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for liraglutide-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies. *TRESIBA® (insulin degludec):* In studies of type 2 diabetes patients, 31.5% of patients who received insulin degludec once daily were positive for anti-insulin antibodies (AIA) at least once during the studies, including 14.5% that were positive at baseline. The antibody incidence rates for type 2 diabetes may be underreported due to potential assay interference by endogenous insulin in samples in these patients. The presence of antibodies that affect clinical efficacy may necessitate dose adjustments to correct for tendencies toward hyper or hypoglycemia. The incidence of anti-insulin degludec antibodies has not been established. **Post-Marketing Experience:** The following additional adverse reactions have been reported during post-approval use. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Liraglutide:* Medullary thyroid carcinoma; Dehydration resulting from nausea, vomiting and diarrhea; Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis; Angioedema and anaphylactic reactions; Allergic reactions: rash and pruritus; Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death; Hepatobiliary disorders: elevations of liver enzymes, hyperbilirubinemia, cholestasis, hepatitis

DRUG INTERACTIONS: Medications that Can Affect Glucose Metabolism: A number of medications affect glucose metabolism and may require dose adjustment of XULTOPHY® 100/3.6 and particularly close monitoring *[see Warnings and Precautions]*.

Drugs That May Increase the Risk of Hypoglycemia	
Drugs:	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
Intervention:	Dose reductions and increased frequency of glucose monitoring may be required when XULTOPHY® 100/3.6 is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of XULTOPHY® 100/3.6	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention:	Dose increases and increased frequency of glucose monitoring may be required when XULTOPHY® 100/3.6 is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of XULTOPHY® 100/3.6	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when XULTOPHY® 100/3.6 is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine, and reserpine
Intervention:	Increased frequency of glucose monitoring may be required when XULTOPHY® 100/3.6 is co-administered with these drugs.

Effects of Delayed Gastric Emptying on Oral Medications: Liraglutide-containing products, including XULTOPHY® 100/3.6, cause a delay of gastric emptying, and thereby have the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, liraglutide did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with liraglutide containing products.

USE IN SPECIFIC POPULATIONS: Pregnancy: Risk Summary: Based on animal reproduction studies, there may be risks to the fetus from exposure to liraglutide during pregnancy. XULTOPHY® 100/3.6 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no available data with XULTOPHY® 100/3.6, insulin degludec or liraglutide in pregnant women to inform a drug associated risk for major birth defects and miscarriage. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy *[see Clinical Considerations]*. For insulin degludec, rats and rabbits were exposed in animal reproduction studies at 5 times (rat) and 10 times (rabbit) the human exposure at a dose of 0.75 U/kg/day. No adverse outcomes were observed for pregnant animals and offspring *[see Data]*. For liraglutide, animal reproduction studies identified increased adverse developmental outcomes from exposure during pregnancy. Liraglutide exposure was associated with an imbalance in some fetal abnormalities in pregnant rats administered liraglutide during organogenesis at doses that approximate clinical exposures at the maximum recommended human dose (MRHD) of 1.8 mg/day and early embryonic deaths at 11-fold clinical exposures at the MRHD. In pregnant rabbits administered liraglutide during organogenesis, decreased fetal weight and an increased incidence of major fetal abnormalities were seen at exposures below the human exposures at the MRHD *[see Data]*. The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA_{1c} >7 and has been reported to be as high as 20–25% in women with a HbA_{1c} >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively. Clinical Considerations: *Disease-associated maternal and/or embryo/fetal risk:* Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity. Data: *Animal Data: Insulin degludec:* Insulin degludec was investigated in studies covering fertility, embryo-fetal development and pre- and post-natal development in rats and during the period of embryofetal development in rabbits. Human insulin (NPH insulin) was included as comparator. In these studies insulin degludec was given subcutaneously at up to 21 U/kg/day in rats and 3.3 U/kg/day in rabbits, resulting in 5 times (rat) and 10 times (rabbit) the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day. Overall the effects of insulin degludec were similar to those observed with human insulin. *Liraglutide:* Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating, during mating and the period of organogenesis, through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misshapen oropharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day. Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased maternal body weight gain during the dosing period. Liraglutide decreased fetal weight and dose dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), ≥ 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group. In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8-, 3-, and 11-times human exposure at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F2 generation rats descended from liraglutide-treated rats compared to F2 generation rats descended from controls, but differences did not reach statistical significance for any group. **Lactation:** Risk Summary: There are no data on the presence of liraglutide or insulin degludec in human milk, the effects on the breastfed infant, or the effects on milk production. In lactating rats, insulin degludec and liraglutide, the two components of XULTOPHY® 100/3.6, were present in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XULTOPHY® 100/3.6 and any potential adverse effects on the breastfed infant from XULTOPHY® 100/3.6 or from the underlying maternal condition. Data: *Insulin degludec:* In lactating rats, insulin degludec was present in milk at a concentration lower than that in plasma. *Liraglutide:* In lactating rats, liraglutide was present unchanged in milk at concentrations approximately 50% of maternal plasma concentrations. **Pediatric Use:** Safety and effectiveness of XULTOPHY® 100/3.6 have not been established in pediatric patients. **Geriatric Use:** Of the total number of 1881 subjects in clinical studies of XULTOPHY® 100/3.6, 375 (19.9%) were 65 years and over, while 52 (2.8%) were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals to the effects of XULTOPHY® 100/3.6 cannot be ruled out. Age had no clinically relevant effect on the pharmacokinetics of XULTOPHY® 100/3.6. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be more difficult to recognize in the elderly. **Renal Impairment:** *XULTOPHY® 100/3.6*: There is limited experience with XULTOPHY® 100/3.6 in patients with mild and moderate renal impairment and when used in these patients, additional glucose monitoring and XULTOPHY® 100/3.6 dose adjustments may be required on an individual basis. XULTOPHY® 100/3.6 has not been studied in patients with severe renal impairment *[see Warnings and Precautions]*. *Insulin degludec:* No clinically relevant difference in the pharmacokinetics of insulin degludec was identified in a study comparing healthy subjects and subjects with renal impairment including subjects with end stage renal disease. *Liraglutide:* The safety and efficacy of liraglutide was evaluated in a 26 week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73 m^2). There is limited experience with liraglutide in patients with severe renal impairment including end stage renal disease. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis *[see Warnings and Precautions and Adverse Reactions]*. **Hepatic Impairment:** *XULTOPHY® 100/3.6:* XULTOPHY® 100/3.6 has not been studied in patients with hepatic impairment. *Insulin degludec:* No clinically relevant difference in the pharmacokinetics of insulin degludec, one of the components of XULTOPHY® 100/3.6, was identified in a study comparing healthy subjects and subjects with hepatic impairment (mild, moderate, and severe hepatic impairment). *Liraglutide:* There is limited experience in patients with mild, moderate or severe hepatic impairment with liraglutide, one of the components of XULTOPHY® 100/3.6. **Gastroparesis:** Liraglutide, one of the components of XULTOPHY® 100/3.6, slows gastric emptying. XULTOPHY® 100/3.6 has not been studied in patients with pre-existing gastroparesis.

OVERDOSAGE: Hypoglycemia (from insulin and liraglutide) and gastrointestinal adverse reactions (from liraglutide) may develop if a patient is dosed with more XULTOPHY® 100/3.6 than required. An excess of insulin-containing products like XULTOPHY® 100/3.6 relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia and hypokalemia *[see Warnings and Precautions]*. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise 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. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia. Hypokalemia must be corrected appropriately. Overdoses have been reported in clinical trials and post-marketing use of liraglutide, one of the components of XULTOPHY® 100/3.6. Effects have included severe nausea and severe vomiting. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

More detailed information is available upon request.

For information about XULTOPHY® 100/3.6 contact:
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PATENT Information: http://novonordisk-us.com/patients/products/product-patents.html

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

novo nordisk®

Xultophy® 100/3.6
insulin degludec 100 units/mL and liraglutide 3.6 mg/mL injection

VICTOZA® (liraglutide) injection
Rx Only
BRIEF SUMMARY: Please consult package insert for full prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether VICTOZA® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions]*. VICTOZA® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of VICTOZA® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with VICTOZA® *[see Contraindications and Warnings and Precautions]*.

INDICATIONS AND USAGE: VICTOZA® is indicated: as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus; to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. Limitations of Use: VICTOZA® is not a substitute for insulin. VICTOZA® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. The concurrent use of VICTOZA® and prandial insulin has not been studied.

CONTRAINDICATIONS: Medullary Thyroid Carcinoma: VICTOZA® is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). **Hypersensitivity:** VICTOZA® is contraindicated in patients with a prior serious hypersensitivity reaction to VICTOZA® or to any of the product components. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with VICTOZA® *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-cell Tumors: Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether VICTOZA® will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. Cases of MTC in patients treated with VICTOZA® have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and VICTOZA® use in humans. VICTOZA® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of VICTOZA® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with VICTOZA®. Such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated. **Pancreatitis:** Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with VICTOZA®. After initiation of VICTOZA, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, VICTOZA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, VICTOZA® should not be restarted. In glycemic control trials of VICTOZA®, there have been 13 cases of pancreatitis among VICTOZA®-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with VICTOZA® were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a VICTOZA®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. VICTOZA® has been studied in a limited number of patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on VICTOZA®. **Never Share a VICTOZA® Pen Between Patients:** VICTOZA® pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens. **Use with Medications Known to Cause Hypoglycemia:** Patients receiving VICTOZA® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin *[see Adverse Reactions]*. **Renal Impairment:** VICTOZA® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in VICTOZA®-treated patients *[see Adverse Reactions]*. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration *[see Adverse Reactions]*. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including VICTOZA®. Use caution when initiating or escalating doses of VICTOZA® in patients with renal impairment *[see Use in Specific Populations]*. **Hypersensitivity Reactions:** There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with VICTOZA®. If a hypersensitivity reaction occurs, discontinue VICTOZA; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity reaction to VICTOZA® *[see Contraindications]*. Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-receptor agonist because it is unknown whether such patients will be predisposed to these reactions with VICTOZA®. **Acute Gallbladder Disease:** In the LEADER trial, 3.1% of VICTOZA®-treated patients versus 1.9% of placebo-treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis. The majority of events required hospitalization or cholecystectomy. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

ADVERSE REACTIONS: The following serious adverse reactions are described below or elsewhere in the prescribing information: Risk of Thyroid C-cell Tumors *[see Warnings and Precautions]*; Pancreatitis *[see Warnings and Precautions]*; Use with Medications Known to Cause Hypoglycemia *[see Warnings and Precautions]*; Renal Impairment *[see Warnings and Precautions]*; Hypersensitivity Reactions *[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. Common Adverse Reactions: The data in Table 1 are derived from 5 glycemic control, placebo-controlled trials. These data reflect exposure of 1673 patients to VICTOZA® and a mean duration of exposure to VICTOZA® of 37.3 weeks. The mean age of patients was 58 years, 4% were 75 years or older and 54% were male. The population was 79% White, 6% Black or African American, 13% Asian; 4% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 9.1 years and a mean HbA_{1c} of 8.4%. Baseline estimated renal function was normal or mildly impaired in 88.1% and moderately impaired in 11.9% of the pooled population. Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of VICTOZA®. These adverse reactions occurred more commonly on VICTOZA® than on placebo and occurred in at least 5% of patients treated with VICTOZA®.

Table 1 Adverse reactions reported in ≥ 5% of VICTOZA®-treated patients

	Placebo N = 661	**Liraglutide 1.2 mg** N = 645	**Liraglutide 1.8 mg** N = 1024
Adverse Reaction	(%)	(%)	(%)
Nausea	5	18	20
Diarrhea	4	10	12
Headache	7	11	10
Nasopharyngitis	8	9	10
Vomiting	2	6	9
Decreased appetite	1	10	9
Dyspepsia	1	4	7
Upper Respiratory Tract Infection	6	7	6
Constipation	1	5	5
Back Pain	3	4	5

Cumulative proportions were calculated combining studies using Cochran-Mantel-Haenszel weights.

In an analysis of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1. Other Adverse Reactions: *Gastrointestinal Adverse Reactions:* In the pool of 5 glycemic control, placebo-controlled clinical trials, withdrawals due to gastrointestinal adverse reactions, occurred in 4.3% of VICTOZA®-treated patients and 0.5% of placebo-treated patients. Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials. *Injection site reactions:* Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of VICTOZA®-treated patients in the five double-blind, glycemic control trials of at least 26 weeks duration. Less than 0.2% of VICTOZA®-treated patients discontinued due to injection site reactions. *Hypoglycemia:* Hypoglycemia requiring the assistance of another person in placebo-controlled trials: In 5 glycemic control, placebo-controlled clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 8 VICTOZA®-treated patients (7.5 events per 1000 patient-years). Of these 8 VICTOZA®-treated patients, 7 patients were concomitantly using a sulfonylurea.

Table 2 Incidence (%) and Rate (episodes/patient year) of Hypoglycemia in 26-Week Combination Therapy Placebo-controlled Trials

	Placebo Comparator	**VICTOZA® Treatment**
Add-on to Metformin	**Placebo + Metformin** (N = 121)	**VICTOZA® + Metformin** (N = 724)
Patient not able to self-treat	0	0.1 (0.001)
Patient able to self-treat	2.5 (0.06)	3.6 (0.05)
Add-on to Glimepiride	**Placebo + Glimepiride** (N = 114)	**VICTOZA® + Glimepiride** (N = 695)
Patient not able to self-treat	0	0.1 (0.003)
Patient able to self-treat	2.6 (0.17)	7.5 (0.38)
Not classified	0	0.9 (0.05)
Add-on to Metformin + Rosiglitazone	**Placebo + Metformin + Rosiglitazone** (N = 175)	**VICTOZA® + Metformin + Rosiglitazone** (N = 355)
Patient not able to self-treat	0	0
Patient able to self-treat	4.6 (0.15)	7.9 (0.49)
Not classified	1.1 (0.03)	0.6 (0.01)
Add-on to Metformin + Glimepiride	**Placebo + Metformin + Glimepiride** (N = 114)	**VICTOZA® + Metformin + Glimepiride** (N = 230)
Patient not able to self-treat	0	2.2 (0.06)
Patient able to self-treat	16.7 (0.95)	27.4 (1.16)
Not classified	0	0

"Patient not able to self-treat" is defined as an event requiring the assistance of another person for treatment.

Papillary thyroid carcinoma: In glycemic control trials of VICTOZA®, there were 7 reported cases of papillary thyroid carcinoma in patients treated with VICTOZA® and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient-years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound. *Cholelithiasis and cholecystitis:* In glycemic control trials of VICTOZA®, the incidence of cholelithiasis was 0.3% in both VICTOZA®-treated and placebo-treated patients. The incidence of cholecystitis was 0.2% in both VICTOZA®-treated and placebo-treated patients. In the LEADER trial, the incidence of cholelithiasis was 1.5% (3.9 cases per 1000 patient years of observation) in VICTOZA®-treated and 1.1% (2.8 cases per 1000 patient years of observation) in placebo-treated patients, both on a background of standard of care. The incidence of acute cholecystitis was 1.1% (2.9 cases per 1000 patient years of observation) in VICTOZA®-treated and 0.7% (1.9 cases per 1000 patient years of observation) in placebo-treated patients. **Laboratory Tests:** *Bilirubin:* In the five glycemic control trials of at least 26 weeks duration, mildly elevated serum bilirubin concentrations (elevations to no more than twice the upper limit of the reference range) occurred in 4.0% of VICTOZA®-treated patients, 2.1% of placebo-treated patients and 3.5% of active-comparator-treated patients. This finding was not accompanied by abnormalities in other liver tests. The significance of this isolated finding is unknown. *Calcitonin:* Calcitonin, a biological marker of MTC, was measured throughout the clinical development program. At the end of the glycemic control trials, adjusted mean serum calcitonin concentrations were higher in VICTOZA®-treated patients compared to placebo-treated patients but not compared to patients receiving active comparator. Between group differences in adjusted mean serum calcitonin values were approximately 0.1 ng/L or less. Among patients with pretreatment calcitonin <20 ng/L, calcitonin elevations to >20 ng/L occurred in 0.7% of VICTOZA®-treated patients, 0.3% of placebo-treated patients, and 0.5% of active-comparator-treated patients. The clinical significance of these findings is unknown. *Lipase and Amylase:* In one glycemic control trial in renal impairment patients, a mean increase of 33% for lipase and 15% for amylase from baseline was observed for VICTOZA®-treated patients while placebo-treated patients had a mean decrease in lipase of 3% and a mean increase in amylase of 1%. In the LEADER trial, serum lipase and amylase were routinely measured. Among VICTOZA®-treated patients, 7.9% had a lipase value at any time during treatment of greater than or equal to 3 times the upper limit of normal compared with 4.5% of placebo-treated patients, and 1% of VICTOZA®-treated patients had an amylase value at any time during treatment of greater than or equal to 3 times the upper limit of normal versus 0.7% of placebo-treated patients. The clinical significance of elevations in lipase or amylase with VICTOZA® is unknown in the absence of other signs and symptoms of pancreatitis *[see Warnings and Precautions]*. **Vital signs:** VICTOZA® did not have adverse effects on blood pressure. Mean increases from baseline in heart rate of 2 to 3 beats per minute have been observed with VICTOZA® compared to placebo. **Immunogenicity:** Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with VICTOZA® may develop anti-liraglutide antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to liraglutide cannot be directly compared with the incidence of antibodies of other products. Approximately 50-70% of VICTOZA®-treated patients in five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these VICTOZA®-treated patients. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the VICTOZA®-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the VICTOZA®-treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 2.3% of the VICTOZA®-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the VICTOZA®-treated patients in the double-blind 26-week add-on combination therapy trials. Antibody formation was not associated with reduced efficacy of VICTOZA® when comparing mean HbA_{1c} of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA_{1c} with VICTOZA® treatment. In five double-blind glycemic control trials of VICTOZA®, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of VICTOZA®-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for VICTOZA®-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies. In the LEADER trial, anti-liraglutide antibodies were detected in 11 out of the 1247 (0.9%) VICTOZA®-treated patients with antibody measurements. Of the 11 VICTOZA®-treated patients who developed anti-liraglutide antibodies, none were observed to develop neutralizing antibodies to liraglutide, and 5 patients (0.4%) developed cross-reacting antibodies against native GLP-1. **Post-Marketing Experience:** The following additional adverse reactions have been reported during post-approval use of VICTOZA®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Medullary thyroid carcinoma *[see Warnings and Precautions]*; Dehydration resulting from nausea, vomiting and diarrhea. *[see Warnings and Precautions]*; Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis. *[see Warnings and Precautions]*; Angioedema and anaphylactic reactions. *[see Contraindications, Warnings and Precautions]*; Allergic reactions: rash and pruritus; Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death *[see Warnings and Precautions]*; Hepatobiliary disorders: elevations of liver enzymes, hyperbilirubinemia, cholestasis, hepatitis *[see Adverse Reactions]*

DRUG INTERACTIONS: Oral Medications: VICTOZA® causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, VICTOZA® did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with VICTOZA®.

USE IN SPECIFIC POPULATIONS: Pregnancy: Risk Summary: Based on animal reproduction studies, there may be risks to the fetus from exposure to VICTOZA® during pregnancy. VICTOZA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal reproduction studies identified increased adverse developmental outcomes from exposure during pregnancy. Liraglutide exposure was associated with early embryonic deaths and an imbalance in some fetal abnormalities in pregnant rats administered liraglutide during organogenesis at doses that approximate clinical exposures at the maximum recommended human dose (MRHD) of 1.8 mg/day. In pregnant rabbits administered liraglutide during organogenesis, decreased fetal weight and an increased incidence of major fetal abnormalities were seen at exposures below the human exposures at the MRHD *[see Animal Data]*. The estimated background risk of major birth defects for women with uncontrolled pre-gestational diabetes (Hemoglobin A_{1C} >7) is 6 to 10%. The major birth defect rate has been reported to be as high as 20 to 25% in women with a Hemoglobin A_{1C} >10. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Clinical Considerations: *Disease-associated maternal and/or embryo/fetal risk:* Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications due to fetal macrosomia (e.g., perineal injury and lacerations, need for cesarean section, and post-partum hemorrhage). Poorly controlled diabetes increases the fetal risk for neural tube defects, cardiovascular malformations, oral clefts, still birth,

macrosomia related morbidity (e.g., brachial plexus injury, hypoxia), and neonatal hyperglycemia. Animal Data: Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misshapen oropharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day. Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), ≥ 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group. In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8-, 3-, and 11-times human exposure at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F_2 generation rats descended from liraglutide-treated rats compared to F_2 generation rats descended from controls, but differences did not reach statistical significance for any group. **Lactation:** Risk Summary: There are no data on the presence of VICTOZA® in human milk, the effects on the breastfed infant, or the effects on milk production. Liraglutide was present in milk of lactating rats *[see Data]*. Developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VICTOZA® and any potential adverse effects on the breastfed infant from VICTOZA® or from the underlying maternal condition. Data: In lactating rats, liraglutide was present unchanged in milk at concentrations approximately 50% of maternal plasma concentrations. **Pediatric Use:** Safety and effectiveness of VICTOZA® have not been established in pediatric patients. VICTOZA® is not recommended for use in pediatric patients. **Geriatric Use:** In the VICTOZA® treatment arms of the glycemic control trials, a total of 832 (19.3%) of the patients were 65 to 74 years of age and 145 (3.4%) were 75 years of age and over. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In the VICTOZA® treatment arm of the LEADER trial, a total of 1738 (37.2%) patients were 65 to 74 years of age, 401 (8.6%) were 75 to 84 years of age, and 17 (0.4%) were 85 years of age or older at baseline. No overall differences in safety or efficacy were observed between these patients and younger patients. **Renal Impairment:** No dose adjustment of VICTOZA® is recommended for patients with renal impairment. The safety and efficacy of VICTOZA® was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m^2). In the VICTOZA® treatment arm of the LEADER trial, 1932 (41.4%) patients had mild renal impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function. There is limited experience with VICTOZA® in patients with end stage renal disease. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis *[see Warnings and Precautions and Adverse Reactions]*. Use caution in patients who experience dehydration. **Hepatic Impairment:** There is limited experience in patients with mild, moderate or severe hepatic impairment. Therefore, VICTOZA® should be used with caution in this patient population. No dose adjustment of VICTOZA® is recommended for patients with hepatic impairment. **Gastroparesis:** VICTOZA® slows gastric emptying. VICTOZA® has not been studied in patients with pre-existing gastroparesis.

OVERDOSAGE: Overdoses have been reported in clinical trials and post-marketing use of VICTOZA®. Effects have included severe nausea and severe vomiting. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

More detailed information is available upon request.

For information about VICTOZA® contact:
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Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

PATENT Information:
http://novonordisk-us.com/patients/products/product-patents.html

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VICTOZA®
liraglutide injection 1.2 mg | 1.8 mg

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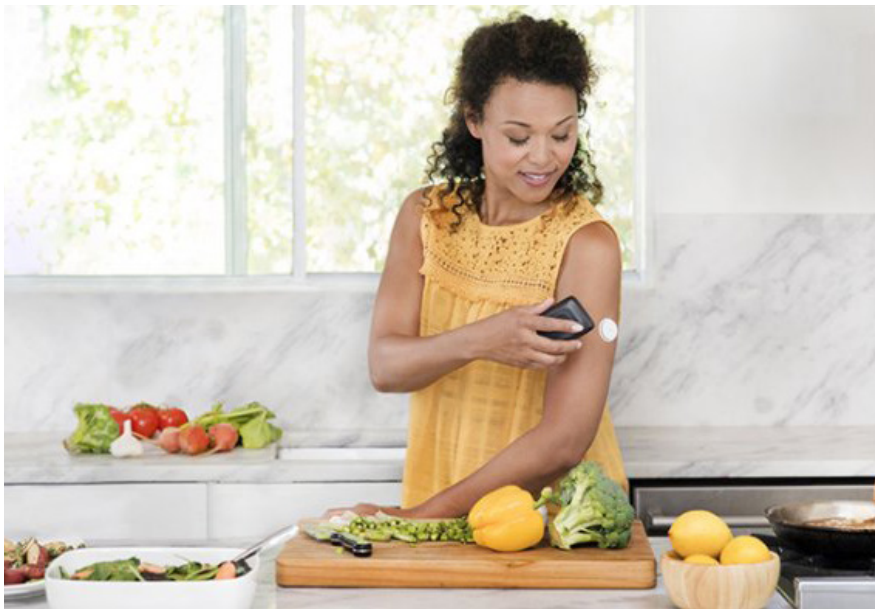


SP571

Abbott's Freestyle Libre Flash glucose monitoring system received FDA approval after being on the market in 40 countries.
Source : Abbott

continued from SP552

Medical World News®

FROM THE CHAIRMAN

Blurring the Lines in Diabetes and Cardiovascular Care

HENNESSY

NEARLY A DECADE AGO, the FDA issued a guidance for the pharmaceutical industry on how to show that new diabetes and obesity therapies did not cause heart attacks or strokes. The result was the cardiovascular outcomes trial, a large, expensive undertaking initially designed to prove that drugs were safe for the highest-risk patients—those who had already suffered heart attack, or who had cardiovascular disease or even conditions like peripheral artery disease. These trials were conceived in crisis, after the blockbuster drug rosiglitazone was linked to heart attacks in a high-profile study in the *New England Journal of Medicine*. So, at first, there was little thought that they would reveal what Yale's Silvio Inzucchi, MD, called the holy grail: a demonstrated cardiovascular *benefit* from a diabetes therapy. Inzucchi offered that tantalizing clue in June 2015 while commenting on another trial; a few months later, he and other investigators unveiled results for EMPA-REG OUTCOME, which showed that the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin cut the risk of cardiovascular death by 32%. During a Peer Exchange at our offices earlier this year, Inzucchi shared his shock at seeing the EMPA-REG OUTCOME data, but today the findings about SGLT2 inhibitors are old news, as the drugs are believed to be a class effect. With results now in from CANVAS for canagliflozin, and real-world data from the CVD-REAL study showing an association between SGLT2 inhibitors and fewer deaths and less hospitalization for heart failure (HF), the lines between diabetes and cardiovascular care for some therapies blurred long ago. The good news is not limited to the SGLT2 inhibitors; both empagliflozin and a glucagon-like-1 (GLP-1) receptor agonist, liraglutide, now have a cardiovascular indication from FDA. As *Evidence-Based Diabetes Management*™ (*EBDM*™) went to press, the FDA acted on a cardiovascular indication for a cholesterol therapy, evolocumab, that will be used by some very high-risk patients with diabetes. Now, trials are under way exploring the potential for SGLT2 inhibitors to treat HF, whether or not patients have diabetes. The potential role for these drugs in primary prevention is more than just a theory. In addition, each year brings more and more crossover between endocrinologists and cardiologists at major scientific meetings in diabetes and cardiovascular care, as the 2 fields share data and perspectives on treating the highest-risk patients. For decades, we've understood there is a connection: the American Heart Association reports that people with diabetes are 2 to 4 times more likely to die from heart disease. But in some ways, we're just finding out how much we don't know about these links, and how much potential exists to do more for patients. As Harvard's Eldrin F. Lewis, MD, MPH, discusses in our cover story on HF and diabetes, the rise of new payment models forced hospitals to think differently about how to care for these vulnerable patients, and that's been better all involved. As Andrew Smith writes, another frontier is finding out how today's diabetes therapies can help prevent costly microvascular outcomes like end-stage renal disease—new trials to examine these questions are under way.

For decades, we've understood there is a connection between diabetes and cardiovascular disease. The American Heart Association reports that people with diabetes are 2 to 4 times more likely to die from heart disease.

We hope you enjoy this special issue of *EBDM*™ on the intersection of diabetes and cardiovascular care. As always, thank you for reading. ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

FROM THE EDITOR-IN-CHIEF

For Those With Diabetes and CV Risk, Personalized Care Matters


GABBAY

IN 1979, THE FRAMINGHAM STUDY told us that people with diabetes are at least twice as likely to develop cardiovascular disease (CVD), putting them at risk for early death from cardiovascular (CV) causes. Since that time, those of us in diabetes care have searched for the right combination of lifestyle management, therapy, and other tools to change this fact. We've made progress, but it remains true that people with diabetes die of heart disease at much higher rates than others, and we don't entirely understand why.

Although we know many of the risk factors that are responsible for diabetes being a cardiovascular risk equivalent, the traditional risk factors (hypertension, hyperlipidemia, and obesity) do not fully explain why the risk of a myocardial infarction (MI) in a patient with diabetes is roughly the same as a typical post-MI patient without diabetes. Precision medicine should be able to identify new risk factors and predictors of coronary disease—the leading cause of mortality for people with diabetes. We must account not only for genetic and environmental factors but also for behavioral and socioeconomic differences, which can predict how well a patient will be able to follow a regimen for the long haul.

We continue to learn. Data gathered a decade ago during Action to Control Cardiovascular Risk in Diabetes (ACCORD) are providing new insights and resolving a puzzle: why did patients at high risk of CVD who had extremely tight glycemic control have a higher rate of fatal heart attacks? Why did they fare worse than their counterparts in standard care? Are there new risk factors that might explain this surprising difference? In other words, those in the group with the most tightly controlled diabetes were less likely to have a heart attack, but if they had one, it was more likely to be fatal.

Last month, scientists led by Joslin Diabetes Center published a paper in *Diabetes Care* that that finds genetic links between glucagon-like peptide-1 (GLP-1) and CV mortality. The team showed how patients in the ACCORD study with a genetic variant associated with CV mortality saw their fasting GLP-1 levels drop while undergoing strict glycemic control. For those without the variant, GLP-1 levels were stable.

The implications of this finding are potentially significant. We already know that GLP-1 agonists can reduce cardiovascular events in people with diabetes. Several GLP-1 receptor agonists have been approved based on their ability to promote insulin production, and 2 have already shown CV benefits in clinical trials. One (liraglutide) received FDA approval in August for a cardiovascular indication with the recently approved semaglutide likely to follow. Furthermore, the genetic variant found in the ACCORD population may represent a new risk factor in explaining the high risk of CVD in individuals with diabetes.

Along with GLP-1 agonists, a second glucose lowering medication, has been shown to decrease cardiovascular events: SGLT2 inhibitors. As we review the findings of the cardiovascular outcomes trials for 2 of the approved sodium glucose co-transporter-2 (SGLT2) inhibitors, there the belief is that they cause diuresis and volume contraction to produce benefits for patients with congestive heart failure, leading to fewer hospitalizations.

Both examples are of interest to payers, who are interested in the right drugs to the right patients, and who want proof that therapies can reduce costs in high-risk populations. The surprising results with SGLT2 inhibitors have sparked a new round of trials to resolve the unanswered questions about their role in heart failure, in patients with and without diabetes.

For all the promise of new therapies, however, the basics of care coordination and meeting patients where they are cannot be overlooked. For patients who live with diabetes and heart disease day after day, the financial cost and personal toll are considerable. At Joslin, sharing these lessons along with the latest science is essential to what we do every day. ◆

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

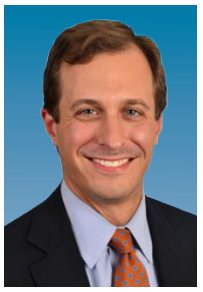
EDITORIAL MISSION

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

REAL-WORLD EVIDENCE

The CVD-REAL Trial: What Can Real-World Evidence Tell Us About Primary Prevention?

Mary Caffrey



CAVENDER

Matthew A. Cavender, MD, MPH, FACC, is an interventional cardiologist and an assistant professor at the University of North Carolina School of Medicine.

IN MARCH 2017, when the first results of the CVD-REAL trial were presented at the American College of Cardiology Scientific Sessions, there was a buzz in the room: This wasn't a randomized clinical trial (RCT), but this could be interesting.

All 3 FDA-approved sodium glucose cotransporter-2 (SGLT2) inhibitors would be compared as a group with other type 2 diabetes (T2D) drugs in a single study, using patient registries or claims data involving over 300,000 patients from 6 different countries. AstraZeneca, maker of the SGLT2 inhibitor dapagliflozin (Farxiga), funded the CVD-REAL study.[1]

The findings, later published in *Circulation*,[2] showed evidence that investigators had wondered about for more than a year: In patients with T2D who were mostly free of established cardiovascular disease (CVD), initiation of an SGLT2 inhibitor was associated with a 51% lower risk of death and a 39% lower risk of hospitalization for heart failure, compared with those initiating another glucose-lowering drug. What's more, despite considerable differences in which SGLT2 inhibitor was predominant in different countries, the results were consistent across the continents—raising the possibility of a class effect.

Although the EMPA-REG OUTCOME trial had surprised clinicians and investigators in 2015 by showing that empagliflozin (Jardiance, Eli Lilly/Boehringer Ingelheim) produced a 38% relative risk reduction in cardiovascular (CV) death,[3] all patients in this study had T2D with established CVD; thus, no conclusions could be made about patients without established cardiovascular disease. But cardiovascular outcomes trials (CVOTs) in the queue at the time CVD-REAL was presented—including CANVAS,[4] for the SGLT2 inhibitor canagliflozin (Invokana, Janssen)—included some of these patients, who have CV risk factors but have not suffered a heart attack or stroke.

Thus, the CVD-REAL study increased the excitement about those trials—and new clinical trials for heart failure just getting under way—because it suggested SGLT2 inhibitors might be useful for patients in earlier stages of T2D.

To understand what this bounty of real-world evidence tells us, and what to expect as CVD-REAL continues, *Evidence-Based Diabetes Management*™ spoke with Matthew A. Cavender, MD, MPH, FACC, an interventional cardiologist at the University of North Carolina and a coauthor of the study who presented additional results during the American Diabetes Association meeting in June.

At that same meeting, the CANVAS investigators reported a 14% reduction in major CV events, including CV death, and said there was no reason to believe the drug behaved any differently between primary prevention patients, who accounted for a third of the study population, and the others.[4] Researchers, payers, and clinicians alike are now looking ahead to DECLARE-TIMI-58, the CVOT for dapagliflozin,[5] as well as new clinical trials that will examine how empagliflozin affects heart failure in patients with and without diabetes.[6,7]

Real-world versus clinical trial data. CVD-REAL is an observational study based on real-world data, and Cavender is very clear on what CVD-REAL says and what it does not say. "The randomized controlled trial is still the gold standard for establishing a clear benefit for establishing definitive evidence of benefit," he said. "However, observational studies are important and play a role in our understanding of the clinical effectiveness of therapies. Observational studies such as CVD-REAL help us fill in holes to understand the potential benefit in patients who were not part of the randomized trials and help us understand whether the benefits seen in randomized trials are translating to clinical practice."

Cavender added, "These benefits, which we see in RCTs, are also being seen in patients in clinical practice, providing evidence that the benefits seen in clinical trials are translating into clinical practice."

Timing and geography. Another important aspect of CVD-REAL, Cavender said, is its timing. It comes between 2 large clinical trials that both studied SGLT2 inhibitors but had different study populations. "Overall, the findings from CVD-REAL are pretty consistent with what was seen in CANVAS," he said. "In CANVAS, two-thirds of the population had established cardiovascular disease, and one-third did not have established cardiovascular disease. In CVD-REAL, the majority of the patients (87%) do not have established cardiovascular disease."

And yet the reductions in hospitalization for heart failure and death are consistent across the 2 study populations, Cavender said.

CVD-REAL is a compilation of studies performed in different countries, with the data merged into a meta-analysis, Cavender explained. The first phase included sites in the United States, the United Kingdom, Sweden, Denmark, Norway, and Germany. Cavender pointed out that consistency in the results between the United States and the European countries is noteworthy.

"The majority of the time evaluated in our first pass of CVD-REAL occurred either immediately before or in the period immediately after the [results of] EMPA-REG OUTCOME [were] released," he said. "One of the things this allowed us to do was look at whether there were variations across geography, since in the United States the majority of the SGTL2 inhibitor use was canagliflozin, and in the European countries the majority of the use was dapagliflozin."

"And what we found was there were no differences [between] the United States or the countries that predominantly used dapagliflozin. While not definitive, this does provide evidence that the associations we're seeing—and the effects we're seeing with canagliflozin in CANVAS, and the effects we're seeing in empagliflozin in EMPA-REG—may not be specific to those drugs, but rather specific to the inhibition of SGLT2. Thus, these associations were seen across the different medications."

Changes over time. Overall, 52.8% of the patients were taking canagliflozin during the study period, while 41.7% were taking dapagliflozin. Because empagliflozin did not reach the market until the end of the initial study period, it accounts for only 5.5% of the patients in the study, but Cavender said this share will increase the next time CVD-REAL reports results, based on Truven Health Analytics data he has seen.[1]

"That's one of the reasons we're interested in continuing to pursue analyses of CVD-REAL. We're looking to see how these associations change over time," Cavender said. Not only will the mix within the SGLT2 class change, he noted, but the drugs in the comparator arm will, too—as more patients take glucagon-like peptide-1 receptor agonists.

Cavender said there's great interest in whether the SGLT2 inhibitor class can prevent heart failure, which remains one of the primary causes of 30-day hospital readmission in the United States.[8] Besides the 3 approved SGLT2 inhibitors, he said, there's

interest in sotagliflozin, a dual SGLT1 and SGLT2 inhibitor. Trial data presented this fall showed the drug helped patients with diabetes lower glycated hemoglobin while using less insulin; patients also experienced improved time in range.[9]

Payers in other countries are interested in real-world data, Cavender said. "I have meetings with regulatory agencies and payers in Asian countries later this year. They are interested in hearing about these results and how they fit into their overall treatment strategies and priorities," he said.

Investigators are currently trying to expand the number of countries that contribute data to CVD-REAL, although they have not been announced. And there's no end date for the research, Cavender said. "As long as we're able to get high-quality clinical data, and as long as we're able to do high-quality analysis, there will be interest," he said. ◆

REFERENCES

1. Caffrey M. Can SGLT2 inhibitors prevent heart failure in a broad population? Results from a real-world study. *Am J Manag Care*. ajmc.com/conferences/acc-2017/can-sglt2-inhibitors-prevent-heart-failure-in-a-broad-population-results-from-a-real-world-study. Published March 19, 2017. Accessed November 24, 2017.
2. Kosiborod M, Cavender MA, Fu AZ, et al. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors). *Circulation*. 2017;136(3):249-259. doi: 10.1161/CIRCULATIONAHA.117.029190.
3. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi: 10.1056/NEJMoa1504720.
4. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. doi: 10.1056/NEJMoa1611925.
5. DECLARE TIMI 58. TIMI Study Group website. timi.org/index.php?page=declare-timi-58. Accessed November 24, 2017.
6. Empagliflozin outcomE tRial in Patients With chrOnic HeaRt Failure With Reduced Ejection Fraction) EMPEROR-Reduced. clinicaltrials.gov/ct2/show/NCT03057977. Updated October 4, 2017. Accessed October 15, 2017.
7. EMPagliflozin outcomE tRial in Patients With chrOnic HeaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved). clinicaltrials.gov/ct2/show/NCT03057951. Updated October 4, 2017. Accessed October 15, 2017.
8. O'Connor CM. High heart failure readmission rates: is it the health system's fault? *JACC Heart Fail*. 2017;5(5):393. doi: 10.1016/j.jchf.2017.03.011.
9. Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes [published online September 13, 2017]. *N Engl J Med*. doi: 10.1056/NEJMoa1708337.

Leading Diabetes Groups Publish Consensus Statement on "Beyond A1C" Measures to Guide FDA, Researchers

Mary Caffrey

AFTER 2 YEARS OF WORK, a consortium of leading diabetes groups has published a statement that group members hope will guide the FDA when it evaluates how drugs and devices affect the everyday health of people with type 1 diabetes (T1D).

The statement, appearing in *Diabetes Care* on November 21, 2017, defines stages of hypoglycemia, hyperglycemia, time in range, and diabetic ketoacidosis. It is a milestone in the "Beyond A1C" movement, an effort by diabetes clinicians and advocates to get regulators—and payers—to recognize management tools based on criteria other than their ability to control glycated hemoglobin (A1C).

Organized by JDRF (formerly the Juvenile Diabetes Research Foundation), the Steering Committee for the Type 1 Diabetes Outcomes Program issued the statement, "Standardizing Clinically Meaningful Outcome Measures Beyond HbA1C for Type 1 Diabetes."[1] The committee includes members of the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), the American Association of Diabetes Educators, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and T1D Exchange.


KOWALSKI

The statement acknowledges what people living with T1D tell clinicians and researchers—while A1C is a useful measure, it fails to capture the day-to-day experience of living with a disease that some describe as a blood sugar roller coaster. JDRF said in a statement that A1C is "the accepted primary outcome measure for glycemic control and evaluating the efficacy of diabetes therapies," but it has limitations. The 3-month average blood glucose measure cannot tell a physician how often a person experiences extreme highs and lows, which can lead to harmful incidents and poor quality of life.

Thus, the "Beyond A1C" movement seeks to give people with T1D better medications, including insulin, and better technology that will keep their blood glucose levels in a healthy target range without the constant adjustments and stress that have characterized older generations of disease management tools.

JDRF Chief Mission Officer Aaron Kowalski, PhD, said in an interview that while the statement is important for creating better frameworks with regulators and payers, the ultimate goal is better clinical care. The statement resolves differences among clinical associations over when hypoglycemia occurs, which will allow advocacy groups to quantify the condition with regulators and allow researchers to compare drugs and devices going forward, he said.

"Having clear definitions, and having all the major stakeholder groups agree—AACE, ADA, the Endocrine Society—now we're all on the same page," Kowalski said.

The next step is working with the FDA to issue a guidance for drug and device developers, which would allow them to put information into a label, Kowalski said. That would be a game-changer with payers—something he has seen clearly in discussions over the artificial pancreas.

"The reduction in hypoglycemia along with hyperglycemia is the big value proposition," Kowalski said. If a person's A1C looks normal but the person has frequent low blood glucose levels, that can go a long way toward making the case for a better device. "If we're able to clearly define that—if we're able to put it in a label—that's going to help," not just with payers but also with healthcare professionals, he said.

Kowalski said the statement's designation of levels of hypoglycemia would be especially valuable, since it would allow future research, as well as FDA labeling, to distinguish if drugs or devices helped patients avoid falling below the Level 2 threshold, which is a blood glucose concentration of 54 mg/dL. The statement distinguishes hypoglycemia levels as the following:

- **Level 1 hypoglycemia.** Defined as a measurable glucose concentration <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L) that can alert a person to take action. Recurrent episodes of hypoglycemia < 70 mg/dL can lead to increased hypoglycemia unawareness, a dangerous condition in which the person with T1D does not sense experience symptoms of hypoglycemia and my not take action. Unawareness increases with age and duration of T1D.
- **Level 2 hypoglycemia.** Defined as a measurable glucose concentration <54 mg/dL (3.0 mmol/L) that needs immediate action. At blood glucose levels below 50 mg/dL, neuroglycemic symptoms and loss of consciousness can occur.
- **Level 3 hypoglycemia**. Defined as a severe event, in which a patient's mental or physical condition is compromised to the point that assistance is needed. The statement reads, "Severe hypoglycemia captures events during which the symptoms associated with hypoglycemia impact a patient to such a degree that the patient requires assistance from others."

Avoiding hypoglycemia is both a health and quality-of-life issue for patients and a cost issue for payers. As the statement notes, chronic episodes of hypoglycemia put a person with T1D at cardiovascular risk and possibly death.

In 2011, *The American Journal of Managed Care*® published the first study that quantified what trips to the emergency department (ED) or hospital admissions cost due to episodes of hypoglycemia. Those estimates, based on data now nearly a decade old, were $17,564 for a hospital admission, $1387 for an ED visit and $394 for an outpatient visit.[2] According to CDC, hypoglycemia accounts for 300,000 ED visits a year. ◆

REFERENCES

1. The Steering Committee for Type 1 Diabetes Outcomes Programs (Kowalski A, corresponding author). Standardizing clinically meaningful outcome measures beyond HbA_{1c} for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. *Diabetes Care*. 2017; 40(12): 1622-1630. https://doi.org/10.2337/dc17-1624.
2. Quilliam BJ, Simeone JC, Ozbay AB, Kogut SJ. The incidence and costs of hypoglycemia in type 2 diabetes. *Am J Manag Care*. 2011;17(10):673-680.

As Trials Report Cardiovascular Outcomes Data, What About Microvascular Results?

Andrew Smith

BUSE

KOSIBOROD

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LARGE CARDIOVASCULAR OUTCOMES trials (CVOTs), designed to show how new diabetes medications affect the incidences of cardiovascular (CV) death, heart attacks, and strokes, also provide limited insight into another area: microvascular complications, such as renal neuropathy and retinopathy.

The data, however, do not tell a consistent story. Glucagon-like peptide 1 (GLP-1) receptor agonists may reduce the overall risk of kidney problems, but at least 1 medication in the class was associated with proliferative retinopathy progression in trial patients. Sodium-glucose co-transporter 2 (SGLT2) inhibitors, on the other hand, appear to reduce the overall risk of kidney problems more than any of the GLP-1 agonists, all without any reported short-term effect on retinopathy. However, the SGLT2 inhibitor, canagliflozin—but no other drug from this class to date—is associated with a higher risk of amputation compared with placebo, although overall rates were small. As for dipeptidyl peptidase-4 (DPP-4) inhibitors, there's no evidence that they have any particular influence on any microvascular outcome (although these outcomes were not rigorously evaluated with these agents in CVOTs).

The strength for all of these vascular findings is far from conclusive, but according to John B. Buse, MD, PhD, there's more evidence of renal protection, particularly for the SGLT2 inhibitors, than damage elsewhere. The ease of measuring creatinine levels ensures that most CVOTs collect regular data on every patient's kidney function, but no CVOT has regularly measured circulation to the eyes and extremities, so the outcome data have come from the very few patients whose adverse events required surgical procedures.

"The CVOTs to date haven't made any effort to systematically measure neuropathy or retinopathy in all patients, and there just aren't enough surgeries to use them as proxies. I suspect the association between some drugs and increased surgeries may stem from the suddenness with which they lower blood sugar," said Buse, a distinguished professor at the University of North Carolina (UNC) School of Medicine who has participated in several CVOTs. "Previous work has shown that fasting blood sugar reductions can exacerbate preexisting eye problems, even though lower blood sugar reduces long-term complications, so doctors might want to take the precaution of starting small and gradually increasing the dose, particularly in poorly controlled patients who already have eye damage. For patients with clinical CV disease, the benefits on heart attack, stroke, and CV death far exceeds these small risks.

"The evidence on kidney function is much more robust, and it shows that both GLP-1 agonists and SGLT2 inhibitors tend to improve outcomes. That said, the findings are not yet strong enough that they should be a major consideration in drug selection," said Buse, who is also the chief of UNC Health Care's Division of Endocrinology and head of its diabetes center. "The main consideration is still what it has always been: getting the patient's A1C [glycated hemoglobin] to target levels of blood sugar control with whatever combination of medications works best for each patient."

GLP-1 Agonists:

- The LEADER trial, which randomized 9340 patients between liraglutide (Victoza) and placebo and followed them for a median period of 3.8 years, made headlines by finding that the GLP-1 analogue was associated with lower rates of stroke, myocardial infarction, and CV death. Less publicized was the fact that liraglutide use was associated with a significant reduction in nephropathy events, which were defined as "a new onset of persistent macroalbuminuria or persistent doubling of serum creatinine level and creatinine clearance per MDRD <45 mL/min/1.73m^2 [Modification of Diet in Renal Disease Study equation] or the need for continuous renal-replacement therapy (in the absence of an acute reversible cause) or death due to renal disease." There were 1.5 such events per 100 patient-years in the liraglutide group and 1.9 per 100 patient-years in the placebo group (HR, 0.78; 95% CI, 0.67-0.92; P = .003). There was no significant difference in retinopathy between the 2 groups and no specific attempt to measure neuropathy by amputations or other vascular outcomes.[1]

- The SUSTAIN-6 trial, which randomized 3297 patients among placebo and 2 doses of semaglutide (a longer-acting version of liraglutide), found that the GLP-1 agonist resulted in significantly less nephropathy than placebo (defined as in the LEADER trial) and significantly more proliferative retinopathy progression (defined as "the need for retinal photocoagulation or treatment with intravitreal agents or vitreous hemorrhage or diabetes-related blindness). Neuropathy events were detected in 62 semaglutide patients and 100 placebo patients (HR, 0.64; 95% CI, 0.46-0.88; P = .005). Retinopathy was detected in 50 semaglutide patients and 26 placebo patients (HR, 1.76; 95% CI, 1.11-2.78; P = .02).[2]

- The ELIXA trial, which randomized 6068 patients between lixisenatide (Adlyxin) and placebo, found that the albumin/creatine ratio in urine samples rose 26% in lixisenatide users (to 11.9 mg/g) and 32% in placebo users (to 13.4 mg/g). Renal and urinary adverse events were also found in fewer lixisenatide patients (12) than placebo patients (20). Neither result rose to the level of significance, however, and there were no data on retinopathy or neuropathy.[3]

- The EXSCEL trial, which randomized 14,752 patients between weekly exenatide (Byetta) and placebo, did not report any microvascular data in the main paper.[4]

SGLT2 Inhibitors

- The EMPA-REG OUTCOME trial, which randomized 7020 patients among 2 doses of the SGLT2 inhibitor, empagliflozin (Jardiance), and placebo, also found evidence of CV benefit, but the initial write-up provided no significant microvascular data. The rate of kidney failure was lower in empagliflozin users than in the placebo group (5.2% vs 6.6%, respectively), but the difference was not significant. The study did not publish any comparative data related to neuropathy or retinopathy.[5]

- The CANVAS program, which followed 10,142 patients who were randomized between canagliflozin (Invokana) and placebo for a mean period of more than 3 years, also found better renal outcomes in the canagliflozin group than in the placebo group. There was a 40% reduction in combined endpoint of estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (HR,

0.60; 95% CI, 0.47-0.77). On the other hand, use of canagliflozin was significantly associated with increased risk of lower extremity amputation. There were 6.3 amputations (mostly toes or metatarsals) per 1000 patient-years in the canagliflozin group and 3.4 amputations per 1000 patient-years in the placebo group (HR, 1.97; 95% CI, 1.41-2.75).[6]

DPP-4 Inhibitors:

- The EXAMINE trial, which followed 5380 patients randomized between alogliptin (Nesina) and placebo, tracked kidney function over a median period of 18 months and found no significant difference between the 2 arms. The study paper did not disclose any data about retinopathy or neuropathy.[7]

- The SAVOR-TIMI-53 trial, which randomized 16,492 patients between saxagliptin and placebo, did not reveal meaningful differences in significant renal events. The study authors did not disclose data on less serious kidney problems or on neuropathy or retinopathy.[8]

- The TECOS trial, which randomized 14,671 patients between sitagliptin (Januvia) and placebo, reported on several types of microvascular outcomes but found little difference between the medication and placebo. Renal failure occurred in 1.4% (100) of sitagliptin patients and 1.5% (111) of placebo patients, which was not a significant difference. Similar numbers of sitagliptin and placebo patients also experienced peripheral arterial disease (2.7% [197] vs 2.9% [209]), amputation (0.8% [60] vs 0.9% [66]), diabetic neuropathy (4.1% [303 vs 3.8% [281]), diabetic blindness (0.3% [24] vs 0.3% [25]), and retinopathy (2.8% [205] vs 2.2% [158]).[9]

Physicians should have more microvascular outcome data to guide their decisions. Another major CVOT, the DECLARE-TIMI-58 trial of dapagliflozin (Farxiga), is expected to report results in 2019. Researchers, moreover, are mining the huge amounts of data generated by existing CVOTs to find additional results. All of the initial papers focused very heavily on the CV outcomes such trials are designed to measure.)

Researchers have already mined data from the EMPA-REG trial for more information about empagliflozin and renal function, and they have found that SGLT2 inhibitor use is associated with slower progression of kidney disease and fewer renal events. New or worsening nephropathy occurred in 525 of 4124 (12.7%) empagliflozin patients and 388 of 2061 (18.8%) placebo patients (HR, 0.61; 95% CI, 0.53-0.70; $P<.001$).[10]

"The renal outcomes analysis from EMPA-REG evaluated several measures of renal disease progression and found that empagliflozin use was consistently associated with relative risk reduction in important renal events of approximately 40%. Analysis of canagliflozin data from the CANVAS program produced similar findings. Although these studies were not specifically designed to evaluate chronic kidney disease [CKD] progression as a primary outcome (most patients in these trials did not have significant CKD at baseline), these results are still pretty compelling," said Mikhail Kosiborod, MD, a professor of medicine at Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City School of Medicine, who was not involved in either EMPA-REG or CANVAS, but is participating in other CVOTs of antidiabetic agents.

"All other things being equal, these findings suggest that, clinically, one might consider an SGLT2 inhibitor for a patient with evidence of early diabetic nephropathy. More data will be generated on this very topic in the next few years, with several dedicated large clinical trial programs currently evaluating the effects of various SGLT2 [inhibitors] on renal outcomes in patients with CKD, regardless of diabetes status."

Other research teams are working to combine data from various trials to perform meta-analyses. The hope, as always, is that truly giant patient populations will create the statistical power needed to reach findings that go beyond the scope of the individual studies.

"The evidence on kidney function is much more robust, and it shows that both GLP-1 agonists and SGLT2 inhibitors tend to impove outcomes. That said, the findings are not yet strong enough that they should be a major consideration in drug selection."

—John B. Buse, MD, PhD,
University of North Carolina School of Medicine

Better still, the makers of empagliflozin and dapagliflozin have already begun new trials in patients with CKD. The first of the trials will have 5000 patients[11] and the second will have 4000 patients.[12] The CREDENCE trial of canagliflozin's renal outcomes, moreover, has already been going on for several years.[13]

There will be limits, however, to the ability of all of this research to answer questions about microvascular outcomes. Many of the trials that are available for researchers to analyze simply did not collect much data on neuropathy or retinopathy, and CVOT patients, depending on the trial, may not be reflective of patients with type 2 diabetes as a whole. Most of them have longstanding and poorly controlled disease that has already led to a CV event, and although their microvascular profiles may be more representative, there's no guarantee that their outcomes will mirror those of other patients.

Despite these limitations, physicians have little reason to expect more robust microvascular data anytime soon. Trials specifically designed to discover how new drugs affect neuropathy and retinopathy seem unlikely. The Diabetes Control and Complications Trial took 10 years to demonstrate the microvascular benefits of a 2 percentage point reduction of A1C levels (in patients with type 1 diabetes).[14] Establishing the benefit, if any, of lesser reductions associated with the use of new medications would likely take longer and cost more, even if the specific effects of those medications improved outcomes by means other than blood sugar reduction, Buse said.

Efforts to mine real-world data can help, but have their own limitations. Coding errors can occur with microvascular outcomes, which may impact the findings. If patients switch medications frequently, as patients with diabetes do, this may complicate interpretation of the results. Even in places like the United Kingdom or Denmark, where most citizens are publicly insured and limited formularies minimize drug switching, it's hard for retrospective analyses to provide a high degree of certainty for microvascular events. ◆

REFERENCES

1. Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375(4):311-322. doi: 10.1056/NEJMoa1603827.

2. Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375(19):1834-1844. doi: 10.1056/NEJMoa1607141.

3. Pfeffer MA, Claggett B, Diaz R, et al; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med.* 2015;373(23):2247-2257. doi: 10.1056/NEJMoa1509225.

4. Holman RR, Bethel MA, Mentz RJ, et al; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2017;377(13):1228-1239. doi: 10.1056/NEJMoa1612917.

5. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128. doi: 10.1056/NEJMoa1504720.

6. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377(7):644-657. doi: 10.1056/NEJMoa1611925.

7. White WB, Cannon CP, Heller SR, et al; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med.* 2013;369(14):1327-1335. doi: 10.1056/NEJMoa1305889.

8. Scirica BM, Bhatt DL, Braunwald E, et al; SAVOR-TIMI-53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* 2013;369(14):1317-1326. doi: 10.1056/NEJMoa1307684.

9. Green JB, Bethel MA, Armstrong PW, et al; TECOS Study Group. Effects of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2015;373(3):232-242. doi: 10.1056/NEJMoa1501352.

10. Wanner C, Inzucchi SE, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med.* 2016;375(4):323-334. doi: 10.1056/NEJMoa1515920.

11. AstraZeneca announces two new phase IIIb trials for Farxiga in chronic kidney disease and chronic heart failure [press release]. Cambridge, UK: AstraZeneca; September 12, 2016. astrazeneca.com/media-centre/press-releases/2016/astrazeneca-announces-two-new-phase-IIIb-trials-for-Forxiga-in-chronic-kidney-disease-and-chronic-heart-failure-120920161.html. Accessed November 27, 2017.

12. Empagliflozin (Jardiance) to be studied in chronic kidney disease [press release]. Ingelheim, Germany, and Indianapolis, IN: Boehringer Ingelheim; June 12, 2017. https://www.boehringer-ingelheim.com/press-release/empagliflozin-be-studied-chronic-kidney-disease. Accessed November 27, 2017.

13. Evaluation of the effects of canagliflozin on renal and cardiovascular outcomes in participants with diabetic nephropathy (CREDENCE). clinicaltrials.gov/ct2/show/NCT02065791. Updated August 28, 2017. Accessed November 27, 2017.

14. Nathan DM; DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care.* 2014;37(1):9-16. doi: 10.2337/dc13-2112.

PROVIDER PERSPECTIVE

Perspectives of a Lipidologist: LDL Cholesterol Testing, PCSK9 Inhibitors

Mary Caffrey

BRINTON

Eliot A. Brinton, MD, FAHA, FNLA, is the president of the Utah Lipid Center in Salt Lake City, Utah, and a past president of the American Board of Clinical Lipidology.

The arrival of therapies that can drive LDL cholesterol to never-imagined levels brings new implications for diabetes care, one of which is the need for a modern cholesterol test. Eliot A. Brinton, MD, FAHA, FNLA, president of the Utah Lipid Center, visited Evidence-Based Diabetes Management™ *this fall to reflect on evidence from 2017 and the challenges of payer coverage for PCSK9 inhibitors.*

OVER THE PAST YEAR, new evidence for the cholesterol-fighting class of therapy called proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has generated discussion about the usefulness of these powerful drugs in diabetes care. The link between diabetes and cardiovascular risk is well known, and this is central to the FDA's 2008 requirement that sponsors of all new glucose-lowering therapies conduct cardiovascular outcomes trials to ensure that these drugs do not cause heart attacks or strokes.[1]

"The whole issue of cardiovascular disease in patients with diabetes is one that we have known of for decades, and it is so important," said Eliot A. Brinton, MD, FAHA, FNLA, president of the Utah Lipid Center in Salt Lake City, in an interview with *Evidence-Based Diabetes Management*™ (*EBDM*™). "It has always been the primary cause of death in patients with type 2 diabetes, and also the primary source of morbidity."

Cholesterol management in diabetes, meanwhile, can be complicated. Diabetic dyslipidemia is a common condition; the best-known form in type 2 diabetes (T2D) is marked by high levels of triglycerides and decreased high-density lipoprotein (HDL) cholesterol. "Changes [are] observed many years before the onset of clinically relevant hyperglycemia," wrote Jonathan D. Schofield, PhD, and his co-authors, in *Diabetes Therapy*. As they explained, these decreased levels of HDL cholesterol are especially relevant clinically for those at high cardiometabolic risk, and this may justify aggressively treating low-density lipoprotein (LDL) cholesterol levels as well.[2]

When PCSK9 inhibitors burst on the scene, the focus was on dramatically reduced levels of LDL cholesterol—up to 60% in clinical trials.[3,4] At first, specific benefits to patients with diabetes were not highlighted. But as Schofield and colleagues wrote in spring 2016, there were suggestions that these patients would benefit as much as patients without diabetes.[2]

Fast forward to 2017, and more PCSK9 inhibitor results are coming in, both for cardiovascular benefits generally and for patients with diabetes specifically. March brought the first results from the FOURIER trial, presented at the American College of Cardiology Scientific Sessions, which found that Amgen's evolocumab, sold as Repatha, reduced major cardiovascular events—first heart attacks, strokes, and cardiovascular death—by 20% overall and by 25% after the first year.[5]

Next, at the American Diabetes Association Scientific Sessions in June, came a pair of results for rival PCSK9 inhibitor alirocumab (Praluent, from Sanofi-Regeneron) that showed a 49% LDL cholesterol reduction for patients with T2D and a 32.5% reduction for patients with dyslipidemia.[6] Finally, follow-up results from FOURIER presented in September at the European Association for the Study of Diabetes Annual Meeting showed that those with diabetes who took evolocumab had a 57% reduction in LDL cholesterol.[7]

An accompanying editorial in *The Lancet* noted, "The focus of cardiovascular disease prevention has shifted from normalization of risk factors to absolute risk reduction. Reducing LDL cholesterol concentration by 1 mmol/L for about 5 years is consistently associated with a 23%-25% lowered risk of major cardiovascular events, with statin and nonstatin therapies alike, irrespective of baseline LDL cholesterol concentration."[8]

The potential to reduce LDL cholesterol to levels never imagined in at-risk patients brought with it the need for more accurate tests, and in September, Quest Diagnostics, the major testing company, announced it would be adopting a test developed at Johns Hopkins University to replace an older method, known as the Friedewald calculation.[9] According to Brinton, the Friedewald method is simply not accurate once LDL cholesterol reaches the levels achieved with PCSK9 inhibitors.

EBDM™ spoke with Brinton about the importance of the new test, what the latest results from FOURIER tell us about LDL cholesterol levels, and payer issues with PCSK9 inhibitors.

Advances in LDL Cholesterol Testing

***EBDM*™: Can you describe the difference between the Friedewald calculation for measuring levels of LDL cholesterol and the new method developed at Johns Hopkins now in use by Quest Diagnostics?**

BRINTON: The Friedewald equation is something that we've used for decades for the calculation of LDL cholesterol. The parameters that are measured are total cholesterol, total triglycerides, and HDL cholesterol. From those 3 measurements, the Friedewald equation will derive an LDL cholesterol level, which is the primary number of interest in terms of the lipid panel and the treatment of lipid disorders.

What has been known for many, many years is that the Friedewald equation is not very accurate. It's kind of one size fits all. The triglyceride levels are divided by 5 to calculate [very low-density lipoprotein] cholesterol; then LDL cholesterol is calculated by difference. This we've known is not a very good calculation. The researchers at Johns Hopkins looked very carefully at the data, where they actually had directly measured LDL—and they said, 'If we directly measured LDL, what is the best equation that would give us the best estimation of that directly measured LDL without having to do a separate measurement?' And they came out with a complicated way of calculating the direct LDL—or calculating LDL as if it were measured directly—and in that process, we've solved some problems.

Specifically, we know Friedewald does not work well when LDL cholesterol levels are low. This is important, because we are becoming much more aggressive in treating LDL levels. With the advent of the PCSK9 inhibitor class we now have on-treatment LDLs of 40 [mg/dL] or 20 [mg/dL] or less. So, we get a much better LDL level in that setting of super-aggressive LDL treatment.

Another setting where the Friedewald performs poorly is with triglycerides that are elevated. In fact, nobody uses Friedewald where the triglycerides are above 400 [mg/dL]. Well, the problem is that long before you get to 400 [mg/dL], the Friedewald is already going off track and not giving us a very good LDL level, and then above 400 [mg/dL] you can't even use it at all. In the setting of high triglycerides, this is a large step forward.

And the reason that's important is 2-fold: (1) High triglycerides are becoming more common, more prevalent, as we have more obesity and more diabetes. Both are becoming more prevalent, in part because of aging of the US population, in part because of

other things that are happening. So, having a more accurate LDL cholesterol in the setting where the triglycerides are approaching, or exceeding, 400 [mg/dL] is extremely helpful. (2) Another development is that we've learned more recently about the importance of hypertriglyceridemia as a risk factor for cardiovascular disease. As we're paying more attention to patients with high triglycerides, we're looking at that triglyceride level, looking at a more accurate calculation of the LDL cholesterol level, which is very, very helpful.

***EBDM™*: Can you discuss the significance of not having to fast before taking this new test?**

BRINTON: Another thing is development of nonfasting versus fasting lipid panels, and specifically triglyceride levels. For the longest time, our standard has been a fasting lipid panel. Recently, studies have shown that a nonfasting lipid panel can be helpful—specifically, nonfasting triglycerides. But also realize that one of the problems of using a nonfasting sample is that this tends to skew the LDL cholesterol level results if you calculate by Friedewald. And so, having a better calculation of LDL in the setting of increasingly popular nonfasting lipid testing is another big advance.

***EBDM™*: Besides a more accurate measure of LDL cholesterol in a nonfasting setting, why does the new test offer greater convenience? Why is this important?**

BRINTON: It's a convenience for the patient to be able to have the testing done nonfasting. Again, our standard is fasting, and there's nothing wrong with fasting. I'm a lipidologist—I do a lot of my testing, even most of my testing, fasting. But for the primary care doctor, for somebody not just focused on lipids per se, it can be very helpful to be able to do a nonfasting [blood] draw and then good lipid panel results. So, for the convenience of the physician in terms of not having to order a test in advance of the visit, or for the patient of not having to fast until 3 or 4 in the afternoon, if that's when the draw is going to take place, it is a major step forward to get accurate results with a nonfasting sample.

***EBDM™*: Is there an advantage for payers?**

BRINTON: The advantages for payers are more indirect, in the sense that there's going to be less redundant lipid testing; maybe we're going to have a better ability to calibrate our treatment. Certainly, with LDL being our primary target of treatment, we're having a renaissance of LDL goals in the United States. It is helpful to the payer to have the doctor understand what is the best estimate of the LDL cholesterol, and therefore, treatment with various pharmaceutical agents. And of course, diet and lifestyle can be better focused where it needs to be focused, if we have a better understanding of how low that patient's LDL cholesterol truly is. Then I think it's easier to use the treatments that are truly necessary or not use the treatments that may not be necessary. So, there is a benefit to the payer for sure, not only a modest benefit in terms of the testing, but also a benefit in terms of the use of the pharmaceuticals.

Perspectives on PCSK9 Inhibitors

***EBDM™*: What do the recent results published in *The Lancet* and presented at the European Society of Cardiology imply about the advantages of PCSK9 inhibitors?**

BRINTON: The FOURIER trial, which was the main study of one of the PCSK9 inhibitors, evolocumab, is a landmark trial. It is the first clinical cardiovascular outcomes trial looking at this new class—there's another on its way; we're going to have results in the next few months—but just taking the FOURIER trial, first, what we see is proof of principle. Adding a PCSK9 to a statin is helpful in terms of additional risk reduction beyond what is available with a statin alone. But then, a very large piece, and this is both clinically and scientifically important, is the question of the relationship between LDL cholesterol measured by whatever means—usually the Friedewald—the relationship between LDL cholesterol on treatment and cardiovascular outcomes. The biggest question here is: Can LDL be too low? Is there harm, or maybe lack of benefit, in having that LDL go ever lower? And the answer from the FOURIER data is "no."[10] The benefit is there, and the harm is not there. There appears to be no such thing as [an LDL] cholesterol that is too low.

[This is] in contrast to glucose, where we have hypoglycemia, a very serious concern clinically, and hypotension, also very serious. [Those] are life-threatening situations if we are not careful. [But] for LDL cholesterol, we don't appear to have any downside for getting that LDL below 40 [mg/dL] or even below 20 [mg/dL]. FOURIER has really given us convincing data for additional benefit and no additional harm, even for an LDL in the less-than-20 [mg/dL] range. We've been concerned about this. I think FOURIER is of an adequate size and adequate power to give us confidence as we go forward to ever-more-aggressive LDL-lowering treatment.

***EBDM™*: At the American College of Cardiology Scientific Sessions in March, physicians took note of the cardiovascular benefits that were seen with Repatha as well as studies that showed the difficulty clinicians experience when prescribing PCSK9 inhibitors.[11] Has the reimbursement experience changed in recent months for this class of therapy?**

BRINTON: We have a wonderful new tool in the field of lipid management and that is this new class of drugs, the PCSK9 inhibitors. They are marvelous because they are so effective in lowering LDL. They work really nicely on top of a statin; if we have someone who is statin-intolerant we are still allowed to use them as long as we have given statins a fair chance. So, then the question is: Can we actually have access to these drugs? And because they are expensive, access has been a big issue. The managed-care people are able to put a few roadblocks in the way—a little extra paperwork—that does make it harder for clinicians to write a PCSK9 inhibitor. Is that getting better? Is it still an issue?

The quick answer is, in my experience, it has changed very little. Maybe we have changed a little in terms of our approach to this, possibly some of the payers are little more relaxed. We do have convincing trial data now with the FOURIER study with evolocumab; we should have similar data soon with the other drug, which is alirocumab. I'm hopeful that this will become less of an issue. But it remains a very important fact that just simply writing a prescription for a PCSK9 inhibitor does not give one immediate access to the drug. On the one hand, we know that we shouldn't just be using this drug widely for everyone who happens to have high cholesterol. On the flip side, if we have patients who really need additional LDL lowering, [if] we have done everything possible with a statin, we're certainly considering, in most of these cases, use of ezetimibe. [That] has now gone generic, so we have greater access to ezetimibe. In the case where patients still have a high residual LDL cholesterol level and they have high residual cardiovascular risk, then adding a PCSK9 inhibitor is a good thing to do, and access remains an important issue. ◆

REFERENCES

1. Guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. FDA website. www.fda.gov/downloads/Drugs/.../Guidances/ucm071627.pdf. Published December 2008. Accessed November 3, 2017.
2. Schofield JD, Liu Y, Rao-Balakrishna P, Malik RA, Soran H. Diabetes dyslipidemia. *Diabetes Ther.* 2016;7(2):203-219. doi: 10.1007/s13300-016-0167-x.
3. Sabatine MS, Giugliano RP, Wiviott SD, et al; Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med.* 2015;372(16):1500-1509. doi: 10.1056/NEJMoa1500858.
4. Robinson JG, Farnier M, Krempf M, et al; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med.* 2015;372(16):1489-1499. doi: 10.1056/NEJMoa1501031.
5. Sabatine MS, Giugliano RP, Keech AC, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med.* 2017;376(18):1713-1722. doi: 10.1056/NEJMoa1615664.
6. Caffrey M. Praluent benefits for diabetes patients seen in pair of PCSK9 studies. *The American Journal of Managed Care®* website. ajmc.com/conferences/ada-2017/praluent-benefits-for-diabetes-patients-seen-in-pair-of-pcsk9-studies. Published June 11, 2017. Accessed November 3, 2017.
7. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomized controlled trial [published online September 14 ,2017]. *Lancet Diab Endocrin.* doi: 10.1016/S2213-8587(17)30313-3.
8. Lotta LA, Griffin SJ. PCSK9 inhibition and type 2 diabetes [published online September 14, 2017]. *Lancet Diab Endocrin.* doi: 10.1016/S2213-8587(17)30321-2.
9. Quest Diagnostics moves to convenient nonfasting cholesterol testing with improved method for assessing heart disease risk and aiding treatment decisions [news release]. Secaucus, NJ: Quest Diagnostics; September 7, 2017. newsroom.questdiagnostics.com/2017-09-07-Quest-Diagnostics-Moves-to-Convenient-Nonfasting-Cholesterol-Testing-with-Improved-Method-for-Assessing-Heart-Disease-Risk-and-Aiding-Treatment-Decisions. Accessed November 2, 2017.
10. Giugliano RP, Pedersen TR, Park JG, et al; FOURIER Investigators. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet.* 2017;390(10106):1962-1971. doi: 10.1016/S0140-6736(17)32290-0.
11. Caffrey M. Data show it's hard to fill PCSK9 prescriptions, confirming cardiologists' complaints. *The American Journal of Managed Care®* website. ajmc.com/conferences/acc-2017/data-show-its-hard-to-fill-pcsk9-prescriptions-confirming-cardiologists-complaints. Published March 19, 2017. Accessed November 3, 2017.

High Blood Pressure Starts at 130/80, New Guidelines Say

Mary Caffrey

HIGH BLOOD PRESSURE BEGINS at a lower point than it once did, now that leading professional societies have released new guidelines for treating hypertension. On November 13, 2017, the American Heart Association (AHA) and the American College of Cardiology (ACC) offered the first major update for treating hypertension since 2003 during the AHA Scientific Sessions in Anaheim, California.

The new guidelines mean about half of Americans (46%) have high blood pressure, up from one-third of US adults, according to Paul Whelton, MD, MSc, and Robert Carey, MD, the chair and vice-chair of the committee, respectively, that updated the guidelines. Whelton, clinical professor of global public health at Tulane University, and Carey, professor of medicine and dean emeritus, School of Medicine, at the University of Virginia, presented the update at a press briefing and later during the sessions.

WHELTON

CAREY

Hypertension occurs when blood puts too much pressure against the walls of the arteries. It is caused by genetic factors; chronic conditions that include obesity, diabetes, and kidney disease; or temporary conditions that include pregnancy or drinking excessive amounts of alcohol.[1] Left uncontrolled, hypertension can cause heart failure and heart attacks. The risk of hypertension rises as people age.

The starting point for high blood pressure will now be a systolic blood pressure (BP) of 130 mmHg and a diastolic BP above 80 mmHg, according to the guidelines, which are based on more than 1000 studies published over the past 3 years but are largely driven by results from SPRINT (Systolic Blood Pressure Intervention Trial), the 2015 study that the National Institutes of Health stopped early because it was so clear that aggressively treating systolic blood pressure to 120 mmHg saved lives.[2]

The new guidelines address "white coat " syndrome and call for patients to take blood pressure readings at home to compare with those taken by a physician.

Whelton and Carey, along with leaders of the ACC and AHA, insisted that even though another 14% of Americans will receive a diagnosis of hypertension under the revised guidelines, only 1.9% more will need prescriptions because the guidelines rely heavily on lifestyle modification. They also called for more team-based medicine and more reliance on telehealth and "between appointment" monitoring of blood pressure—including getting patients to take their blood pressure at home.

"The patient becomes the center of care," said Mary Norine Walsh, MD, FACC, president of the ACC, noting the emphasis on lifestyle change instead of medication.

Whelton acknowledged that getting Americans to change their eating and exercise habits is a tall order. But just because it's hard doesn't mean that the nation's medical community—and patients—shouldn't try. "Lifestyle management is a challenge," he said. "But that's the underlying issue for high blood pressure, and we have to come to grips with it."

The guidelines are 106 specific recommendations across 15 sections that cover a range of patients—from those whose systolic BP has just crossed 120 mmHg to those who are elderly with many comorbidities.[3] AHA and ACC leaders called them the most comprehensive update since the Joint National Committee 7 guidelines of 2003. Key changes in the guidelines include:

FIGURE. Blood Pressure Categories

Blood Pressure Category	Systolic mm Hg (upper #)		Diastolic mm Hg (lower #)
Normal	less than 120	and	less than 80
Elevated	120–129	and	less than 80
High Blood Pressure (Hypertension) Stage 1	130–139	or	80–89
High Blood Pressure (Hypertension) Stage 2	140 or higher	or	90 or higher

Source: American Heart Association: Used with permission

- The category of prehypertension is eliminated. Systolic BP above 120 mmHg and below 130 mmHg, with diastolic BP below 80 mmHg, is considered **elevated.** A lifestyle intervention is recommended, and patients should be reevaluated in 3 to 6 months.
- **Stage 1 hypertension** covers systolic BP of 130 to 139 mmHg and diastolic BP of 80 to 89 mmHg. Here, however, lifestyle intervention remains the recommendation unless the patient also has elevated risk for atherosclerotic cardiovascular disease. Then medication is recommended.
- **Stage 2 hypertension** begins at systolic BP of 140 mmHg and diastolic BP of 90 mmHg. Recommendations call for both lifestyle interventions and medication.[3]

The AHA plans a media campaign, including spots produced by the Ad Council, to promote both the new guidelines and the need for Americans to be aware of the dangers of hypertension, especially its lack of symptoms. Presenters were unclear how they planned to resolve inconsistencies between these new recommendations and others endorsed by primary care physicians, who perform most of the day-to-day care for hypertension.

And the guidelines are specific about what constitutes a healthy lifestyle: It starts with the DASH diet (Dietary Approaches to Stop Hypertension), which promotes fruits and vegetables, low-fat or nonfat dairy, whole grains, and less than 1500 mg of daily sodium intake. The guidelines also call for limiting alcohol to no more than 2 drinks a day for men and no more than 1 per day for women and exercising at least 30 minutes 3 times per week.

When asked how the guidelines committee arrived at 130 mmHg as its target, Carey said the panel weighed going to 120 mmHg but felt that could cause "untoward side effects if we had a lower universal target."

Finally, the guidelines include recommendations on the proper way to measure blood pressure. There had been some controversy over the SPRINT trial because of the way the measurements were taken, as some critics felt they did not resemble the real-world methods of a busy practice. The new guidelines call for taking a patient's BP more than once before diagnosing high blood pressure, and the emphasis on out-of-office readings is designed to address "white coat" syndrome—when patients have high readings because they are nervous in the physician's office.

American Medical Association President David O. Barbe, MD, said the group was "renewing its call" for American adults to take steps to get their blood pressure under control.

"High blood pressure can often be managed effectively when patients work with their physician to create a treatment plan that focuses on healthy lifestyle changes such as exercising, eating a healthy diet, reducing salt intake, drinking alcohol in moderation, losing weight if overweight, and using anti-hypertensive medication when needed," Barbe said in an e-mailed statement. "We encourage people to take action today to get their blood pressure under control by adopting a treatment plan that can help them prevent the lasting, negative health impacts of uncontrolled high blood pressure, including heart attack and stroke." ◆

REFERENCES

1. High blood pressure (hypertension). Mayo Clinic website. mayoclinic.org/diseases-conditions/high-blood-pressure/basics/causes/con-20019580. Published September 9, 2016. Accessed November 20, 2017.

2. Wright JT, Williamson JD, Whelton PK, et al; SPRINT Research Group. A randomized trial of intensive versus standard blood pressure control. *N Engl J Med.* 2015;373(22):2103-2116. doi: 10.1056/NEJMoa1511939.

3. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/APhA/ASH/ASPC/PCNA guideline for the prevention, detection, evaluation and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published online November 13, 2017]. *Hypertension.* doi: 10.1161/HYP.0000000000000065.

When Medication Adherence Improves, but Outcomes Don't Change

EBDM™ *Staff*

THE BEST DRUGS DON'T work if patients don't take them—thus describes the problem of medication adherence, which can happen because patients don't like adverse effects, can't afford co-payments, or simply forget.

So what happens if an intervention gets more patients to take their medication, but their clinical outcomes don't budge? That's what investigators from Brigham & Women's Hospital and Harvard Medical School asked after doing just that, and their results were presented on November 14, 2017, at the American Heart Association Scientific Sessions in Anaheim, California.

The investigators cite 20 years' worth of research showing that half the patients with chronic cardiometabolic conditions—such as hypertension, diabetes, and dyslipidemia—fail to take medication as prescribed; more recent estimates from IMS Health that show this costs the US health system at least $100 billion a year in preventable costs.

"We know this is a major problem that everybody in the healthcare ecosystem now understands," said Niteesh K. Choudhry, MD, PhD, of Brigham and Women's and Harvard, in an interview with *Evidence-Based Diabetes Management*™, as he discussed the findings.

CHOUDHRY

The rise of accountable care organizations has brought many ideas for improving adherence, but results have been mixed. "Most of the interventions that are out there have only been modestly effective, and even the ones that are effective have problems with sustainability or scalability—they're often expensive," Choudhry said.

With this in mind, Choudhry and his colleagues designed an intervention that combined both technology and team-based care—using pharmacists to call patients. As he explained, there were several purposes: come up with an intervention that worked but was also scalable. The result was STIC2IT, or Study of a Tele-Pharmacy Intervention for Chronic Disease to Improve Treatment Adherence, a randomized controlled trial whose results Choudhry presented.

STIC2IT had several important features: It was targeted to the right patients. It used technology, including text messages alongside the phone calls, to make the program more efficient. It used behaviorally tailored interviews conducted by pharmacists to identify individual barriers to adherence. The phone calls were long—at least 20 minutes—and at times uncovered things like the fact that patients who'd been labeled nonadherent in claims data actually were taking their medication or had been told by a doctor to stop.

A total of 4076 patients were randomized but in an intent-to-treat design, as investigators knew not all patients who were offered the intervention would accept it, just like a real-world situation. After 12 months, the overall intervention group had improved their adherence by 4.7%, and among those who accepted the intervention, adherence improved 10.4%. "Overall, that's a pretty big effect for adherence," Choudhry said.

But here's the rub: Disease control didn't change.

"We see this disconnect," he said. "A moderately large improvement in adherence, certainly bigger than we expected going into the study—with no commensurate change in clinical outcomes. This is a strategy to improve adherence, yes. But this may not be all that is necessary to improve actual clinical outcomes."

There were differences among subgroups: Patients with hypertension saw the greatest improvement, with adherence improving 8.5% overall, followed by a 4.6% rise for those with dyslipidemia. Those with diabetes, the smallest group, saw a small decline of 0.2%.

If a pillar of population health strategy is getting patients to take their medication, what do these results tell us? "I think it tells us a couple of different things," Choudhry said. "First of all, the relationship between adherence and outcomes is not as clear as we think it is."

A second lesson is that for patients with poorly controlled chronic disease, adherence by itself may not get the job done. Finally, while this specific intervention might work for some patients, it might not work for everyone—some might need more help. "Ultimately, as we move forward, with improved adherence and improved chronic disease outcomes, we need a combination of things. And we need to be able to identify who needs what. What I need may be very different from what you need," he said.

The next step will be to develop predictors of which strategies will work for which patients—a "personalized medicine" approach to adherence intervention, Choudhry said. "Right now, we don't have those answers." ◆

REFERENCE

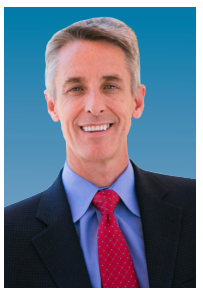
Choudhry NK, Lauffenburger JC, Gopalakrishnan C, et al. Results of the Study of a Tele-Pharmacy Intervention for Chronic Diseases to Improve Treatment Adherence (STIC2IT). Presented at: 2017 American Heart Association Scientific Sessions; November 11-15, 2017; Anaheim, CA. Session LBS-06.

Investigators Dig Deeper on SGLT2 Inhibitors and Find Plenty of News

Mary Caffrey

THE BIG NEWS ON sodium glucose cotransporter-2 (SGLT2) inhibitors may already be out: These therapies for type 2 diabetes (T2D) appear to have a class effect that reduces cardiovascular (CV) risk through a unique mechanism of action that investigators are still trying to understand.

After digging deeper into the data from 2 of the most important diabetes trials of recent years—EMPA-REG OUTCOME, the 2015 cardiovascular outcomes trial for empagliflozin, and CANVAS (the CANagliflozin Cardio-Vascular Assessment Study), the June 2017 counterpart for canagliflozin—investigators appearing on November 13, 2017, at the American Heart Association Scientific Sessions in Anaheim, California, shared results that have implications for some of the highest-risk patients, as well as others with less risk.



MAHAFFEY

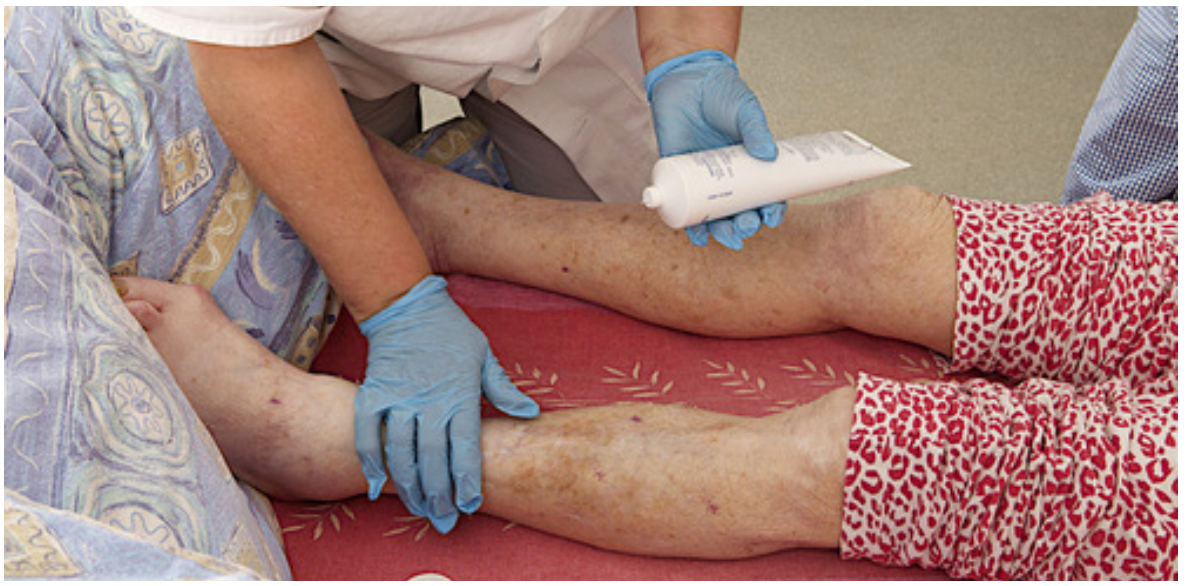
The populations in the 2 cardiovascular outcomes trials reported to date differed in a key way: A third of the 10,142 patients in CANVAS (sold as Invokana by Janssen) did not have a history of CV disease, while all the 7020 patients in the EMPA-REG OUTCOME trial did. When results for CANVAS were reported in June, the study's lead author said that there was no indication the drug was behaving differently in the 2 populations.[1]

In presenting new findings for canagliflozin, Kenneth W. Mahaffey, MD, of Stanford University, put data behind that statement: The results showed that the SGLT2 inhibitor was effective in reducing the risk of CV outcomes in patients with and without a prior history of cardiovascular disease. Patients in the primary prevention group—those with CV risk factors but no disease—had a hazard ratio (HR) of 0.98 (95% CI, 0.74-1.30), while those in the secondary prevention group—those with a history of CV disease—had an HR of 0.82 (95% CI, 0.72-0.95).[2]

In a statement, James F. List, MD, PhD, Janssen global therapeutic area head of Cardiovascular & Metabolism, said, "All people with type 2 diabetes have an increased risk of developing cardiovascular and renal diseases. This new CANVAS analysis is clinically important because it shows that Invokana may offer a broad range of patients an effective treatment option to reduce their risk of cardiovascular and renal disease."[3]

The study's authors, reporting in the journal *Circulation* concluded, "Canagliflozin reduced cardiovascular and renal outcomes with no statistical evidence of heterogeneity of the treatment effect across the primary and secondary prevention groups."[2]

A discussant at the session, Angelyn Bethel, MD, addressed the lack of separation in the curves for the CV outcomes in the primary prevention group in CANVAS. As a trial to find out whether the drug was safe, she said, it was never designed or powered to answer the question of whether the SGLT2 inhibitor could be used widely for prevention. Other results have raised that question, including the recent CVD-REAL findings, which cited a reduction in CV deaths and heart failure hospitalization for patients using SGLT2 inhibitors, based on registry and claims data from more than 300,000 patients.[4]



Follow-up results for SGLT2 inhibitors presented at the 2017 American Heart Association Scientific Sessions included results from CANVAS showing that canagliflozin has similar benefits across a range of groups, and results from EMPA-REG OUTCOME showing that empagliflozin showed reduced cardiovascular risk for patients with peripheral artery disease. Patients with this condition require extra care to avoid amputations.

At the same session, new results for empagliflozin (sold as Jardiance by Boehringer Ingelheim and Eli Lilly) showed substantial benefits for patients with peripheral artery disease (PAD), a serious complication of T2D that can lead to amputations. Patients with PAD accounted for 21% of the study population in EMPA-REG, and these patients experienced even greater reductions in CV events, including CV death, than did the overall study group. Patients with PAD in the trial experienced:

- A 43% reduction in CV death
- A 44% reduction in hospitalization for heart failure
- A 38% reduction in death for any cause
- A 16% reduction in 3-point major adverse cardiovascular event, which includes CV death, non-fatal heart attack, and non-fatal stroke
- A 46% reduction in new or worsening kidney disease[5]

Canagliflozin's benefits for renal outcomes are of great interest to investigators too. A separate trial, called CREDENCE, is fully enrolled and will look specifically at canagliflozin in patients with diabetic nephropathy.[6] Bethel said the research community looks forward to those results—as well as the results of DECLARE (Dapagliflozin Effect on CardiovascuLAR Events), the cardiovascular outcomes trial for dapagliflozin (Farxiga, AstraZeneca)—for more insights on the question of primary prevention.[7] ◆

REFERENCES

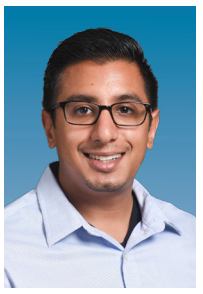
1. Caffrey M. CANVAS finds lower risk of CV events for Invokana. *Am J Manag Care.* ajmc.com/conferences/ada-2017/canvas-finds-lower-risk-of-cv-events-for-invokana. Published June 12, 2017. Accessed November 20, 2017.
2. Mahaffey KW, Neal B, Perkovic V, et al. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program [published online November 13, 2017]. *Circulation.* doi: 10.1161/CIRCULATIONAHA.117.032038.
3. Invokana (canagliflozin) demonstrates cardiovascular (CV) risk reductions in type 2 diabetes patients with and without a history of prior CV events [press release]. Raritan, NJ, and Anaheim, CA: PR Newswire; November 14, 2017. prnewswire.com/news-releases/invokana-canagliflozin-demonstrates-cardiovascular-cv-risk-reductions-in-type-2-diabetes-patients-with-and-without-a-history-of-prior-cv-events-300555488.html?tc=eml_cleartime. Accessed November 14, 2017.
4. Kosiborod M, Cavendar MA, Fu AZ, et al; CVD-REAL Investigators and Study Group. Lower risk of heart failure and death in patients initiated on SGLT2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). *Circulation.* 2017;136(3):249-259. doi: 10.1161/CIRCULATIONAHA.117.029190.
5. Verma S, Mazer CD, Fitchett D, et al. Empagliflozin reduces mortality and hospitalization for heart failure in patients with type 2 diabetes and peripheral artery disease: a sub-analysis of the EMPA-REG OUTCOME trial. Presented at: 2017 American Heart Association Scientific Sessions; November 11-15, 2017; Anaheim, CA. Session LBS-3.
6. Janssen initiates CREDENCE study in patients with type 2 diabetes and diabetic neuropathy [press release]. Raritan, NJ: Johnson & Johnson; February 21, 2014. www.investor.jnj.com/releasedetail.cfm?releaseid=827412. Accessed November 20, 2017.
7. DECLARE-TIMI 58. TIMI Study Group website. timi.org/index.php?page=-declare-timi-58. Accessed November 20, 2017.

Team-Based Pathway Brings Reduction in Heart Failure Readmissions

EBDM™ *Staff*

WHEN CMS STARTED penalizing hospitals that readmitted too many patients within 30 days of discharge, heart failure patients were those most in need of attention. These patients tend to be older and have other health issues, and under the traditional fee-for-service payment systems, there was little incentive to find ways to keep them from coming back after discharge.

By 2015, 30-day readmission was a $17 billion problem for Medicare and Medicaid, and heart failure was the most common cause. It's a problem tied to socioeconomic factors, but that's not the whole story: Current estimates find that about 20% of heart failure patients are readmitted within 30 days and 50% within 6 months.[1]



BHAKTA

But hospitals can turn things around quickly with the right approach. At the 2017 American Heart Association (AHA) Scientific Sessions, in Anaheim, California, Amar Bhakta, MD, of Rush University Medical Center in Chicago, Illinois, presented results from his hospital's clinical pathway for heart failure. Preventing readmissions starts the moment the patient enters the emergency department and involves a multidisciplinary team, help from outside the hospital, and most of all, a plan to ensure follow-up with the patient's primary care physician.

A chart review for 2016 shows the results: From January 1, 2016, to June 30, 2016, before the pathway took effect, the 30-day readmission rate for heart failure patients was 22.5% (88 of 393 patients). From July 1, 2016, through December 31, 2016, the rate was 16.6% (61 of 367 patients).[2]

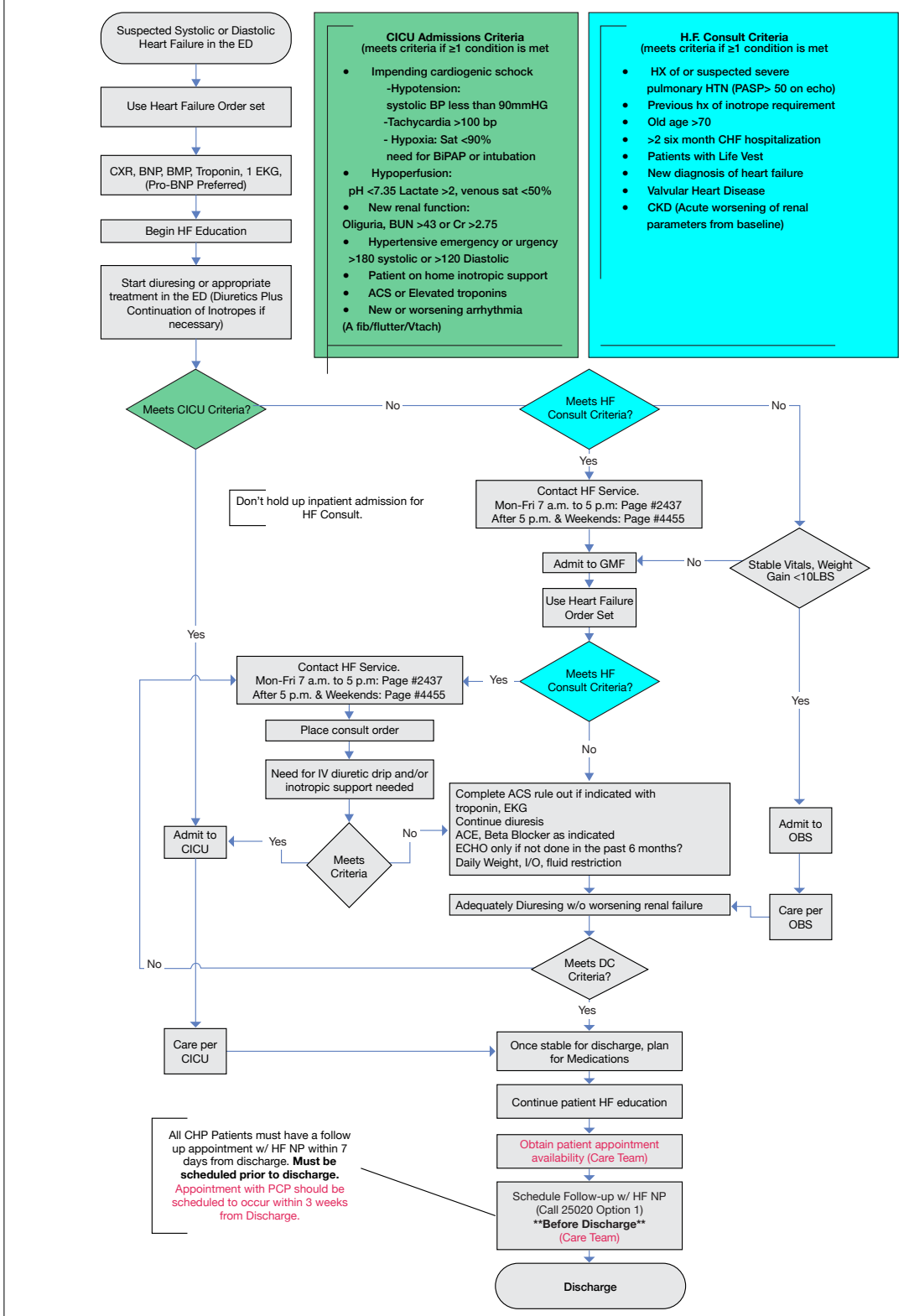
Rush's pathway involves professionals from across the health system: social workers, nurses, nurse practitioners, pharmacists, physicians, hospitalists, heart failure physicians, and administrators. The pathway features standardized admission orders, specific medications, heart failure consult criteria, and criteria for admission to the cardiac intensive care unit, which were included in the abstract presented at AHA. The detailed chart spells out when additional consults with the heart failure specialists occur, what happens if patients gain or lose weight, and what to do given certain renal outcomes.

The critical element of the pathway is the follow-up process: Patients leave the hospital with plans to see a nurse practitioner within 7 days of discharge and their primary care physician within 3 weeks. In an interview with *The American Journal of Managed Care®*, Bhakta said for the population that Rush serves, this second part isn't always easy. But the focus shows in the results: The mean time to follow-up fell from 13 days, (± 1.51 days) in the first 6 months of 2016 to just 8 days (± 0.92 days) in the second 6 months.

Changing reimbursement models are driving much of the change, Bhakta said.

"It's getting most hospitals into a different way of thinking, not just from a reimbursement perspective but also from a patient-centered perspective," he said. "Patients don't want to be readmitted if they're experiencing symptoms. If hospitals aren't being reimbursed, whatever can be done in an appropriate way should be done." ◆

FIGURE. Heart Failure Clinical Pathway at Rush University Medical Center



Source: American Heart Association. Used with permission.

REFERENCES

1. O'Connor CM. Heart failure readmission rates: is it the health system's fault? *JACC Heart Fail.* 2017;5(5):393. doi: 10.1016/j.jchf.2017.03.011.

2. Moseley A, Accavitti MJ, Bhakta A, et al. Reducing heart failure readmissions using a multidisciplinary approach. Presented at: 2017 American Heart Association Scientific Sessions; November 11-15, 2017; Anaheim, CA; Abstract M4062.

Animas Leaves the Insulin Pump Market Amid Competitive Pressures

EBDM™ *Staff*

ANIMAS CORPORATION, part of Johnson & Johnson Diabetes Care, has left the insulin pump market amid market pressures and emerging technology trends.

"We are incredibly grateful to our patients and healthcare partners for the trust, confidence, and loyalty they have placed in Animas products over the last 12 years," said Valerie Asbury, Animas general manager, in statement released October 5, 2017.[1] "With rapidly changing needs of customers, rapidly evolving market dynamics, and increased competitive pressures, it proved too difficult to sustain the insulin pump business, and we decided to pursue an exit of the business."

Animas ended sales of its Vibe and OneTouch Ping pumps in the United States and Canada but said it would honor warranties. Thus, a patient who needs a replacement pump will be able to get one, said Bridget Kimmel, senior manager for communications and public affairs for Johnson & Johnson Diabetes Solutions, in an interview with the *American Journal of Managed Care®*. Decisions about the exit in other countries require consultation with work couÍncils, she said.

Kimmel said the majority of Amimas' 90,000 pump users are within the 4-year warranty period, and most will be within warranty through September 30, 2019.

As previously reported in *Evidence-Based Diabetes Management™*, the insulin pump market faces multiple pressures. First, an exclusivity agreement between market leader Medtronic and the nation's largest payer, UnitedHealthcare, was seen by analysts as a threat to at least 1 of the smaller players in the market.[2] Kimmel said the Medtronic exclusivity agreement with UnitedHealthcare was among many factors that contributed to the decision.

Second, emerging technology such as smart insulin pens and smaller sensors will pair with smarter apps to allow most of the heavy lifting to be done by a patient's smartphone.[3] This could make traditional insulin pumps obsolete. Steven R. Pacelli, executive vice president for Strategy & Corporate Development at Dexcom, which makes popular continuous glucose monitoring systems, told attendees at a Wall Street healthcare conference in September this is a key reason why his company does not want to be in the pump business.[4]

Nonetheless, Dexcom had a relationship with Animas, which received FDA approval less than a year ago for its Vibe pump to integrate with Dexcom's G5.[5] Back in 2010, Animas announced a major initiative with JDRF, formerly the Juvenile Diabetes Research Foundation, to work with Dexcom on artificial pancreas technology. JDRF has decried payer exclusivity deals, saying they would lead to a loss of patient choice. The group released a statement, which read in part:

"JDRF is extremely concerned that Animas Corporation will be closing operations and ending the sale of its insulin pumps, as it means fewer treatment options for people with type 1 diabetes," the statement said. "Pump choice is critical, and people with type 1 diabetes need the ability to choose the devices that work best for them. Innovation and competition are essential to the development of next-generation therapies, and until there's a cure, JDRF will continue to drive efforts that will improve health outcomes for people facing the daily burdens and dangers of this disease."[6]

Earlier this year, Roche left the market and turned its patients over to Medtronic, and Animas announced a similar arrangement. "Patients using an Animas insulin pump will be offered the option to transfer to a Medtronic pump," the Animas statement said.[1,2]

Johnson & Johnson had announced in January it was considering a sale of all its diabetes businesses, which include Animas and LifeScan, which makes blood glucose monitoring systems and a disease management app.[7] Disease management tools are making their way into larger shares of the population with type 2 diabetes (T2D), which in the United states accounts for all but 1.25 million of the 30.3 million people who have the disease.

While the statement said, "Johnson & Johnson is continuing to evaluate potential strategic options for LifeScan, Inc," Kimmel said that for now, it's "business as usual" for the company.

LifeScan, which has a partnership with WellDoc, created the BlueStar technology to provide 24/7 coaching for people with T2D. Also, LifeScan is moving ahead with plans to expand its OneTouch Reveal app across several countries, including India, through the end of 2017, and to promote data-sharing relationships with physicians and managed care companies.[7] Kimmel said a new population health venture with Express Scripts is up and running. ◆

REFERENCES

1. Animas Corporaton to close operations and exist insulin pump market [press release]. Chesterbrook, PA: Johnson & Johnson; October 5, 2017. www.jnj.com/media-center/press-releases/animas-corporation-to-close-operations-and-ex-it-insulin-pump-market. Accessed October 17, 2017.
2. Smith A. UnitedHealthcare's Medtronic deal sparks furor, but a year later, innovation continues. *Am J Manag Care®*. 2017;23(SP11):SP455-SP456.
3. Smith A. After 20 years of watching diabetes tech, Kliff eyes smart insulin pens, CGM for patients with type 2 diabetes. *Am J Manag Care®*. 2017;23(SP11):SP453-SP454.
4. Caffrey M. Fitbit, Dexcom to put CGM on the wrists of people with diabetes. *Am J Manag Care®*. www.ajmc.com/newsroom/fitbit-dexcom-to-put-cgm-data-on-wrists-of-people-with-diabetes. Published September 11, 2017. Accessed October 17, 2017.
5. OneTouch Vibe pump earns FDA approval and Health Canada license and is first pump integrated with the Dexcom G5 mobile continuous glucose monitor [press release]. Chesterbrook, PA: PR Newswire; December 20, 2016. www.prnewswire.com/news-releases/onetouch-vibe-plus-insulin-pump-earns-fda-approval-andhealth-canada-license-and-is-first-pump-integrated-with-the-dexcom-g5-mobilecontinuous-glucose-monitor-300381728.html. Accessed August 20, 2017.
6. JDRF statement: Animas exits the insulin pump business. New York, NY: JDRF; October 5, 2017. www.jdrf.org/blog/2017/10/05/jdrf-statement-animas-exits-the-insulin-pump-business/. Accessed October 17, 2017.
7. Caffrey M. J&J's OneTouch Reveal: connecting diabetes patients with physicians, managed care. *Am J Manag Care*. 2017;23(SP11):SP444.

FDA Approves Continuous Glucose Monitor That Doesn't Require Finger Sticks

Mary Caffrey

PEOPLE WITH DIABETES who live in the United States can finally monitor blood glucose levels without routine finger sticks. The FDA approved Abbott's Freestyle Libre Flash Glucose Monitoring System on September 27, 2017—a decision considered a breakthrough by diabetes advocates long awaiting the approval. The device is already on the market in more than 40 countries.[1]

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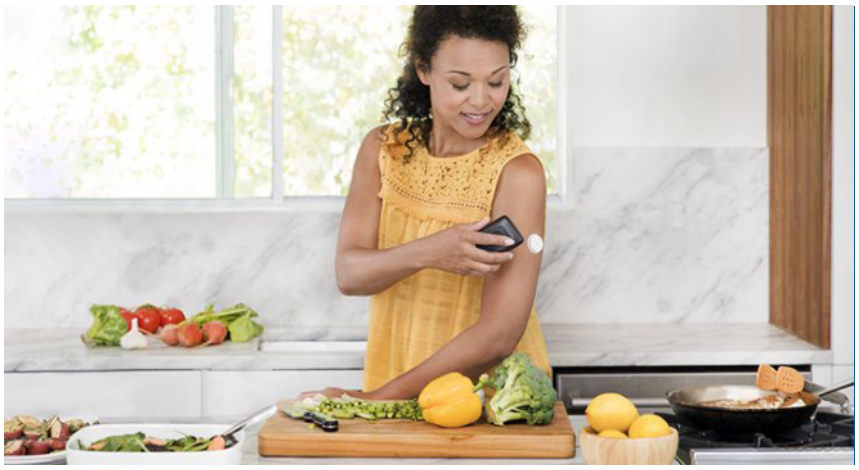
When first approved, continuous glucose monitoring (CGM) systems required patients to conduct a blood glucose test with each insulin dose and to use blood testing to calibrate the system. But as accuracy improved, patients began dosing their insulin based on CGM information without a separate blood test, even though the FDA had not approved the systems for this purpose. That changed earlier this year, when the Dexcom G5 was approved for insulin dosing with calibration twice daily, paving the way for Medicare reimbursement.[2]

The Abbott device, by contrast, is factory calibrated; a sensor wire inserted beneath the skin surface constantly monitors glucose levels. Patients can wave a mobile reader over the device to determine if their blood glucose levels are in range, too high, or too low and check their status over the past 8 hours.

Not only do many patients find frequent finger-stick tests painful and a hassle, but payers often limit the number of test strips they will cover, putting patients in a bind if they need to do a test with every insulin dose or to calibrate the CGM. This newest option cuts down on blood glucose tests and can save patients money.

"We are celebrating a breakthrough moment for people with diabetes in the US—an end to the worry and hassles associated with routine finger sticks, which have been the standard of glucose testing for more than 40 years," Jared Watkin, senior vice president of Abbott Diabetes Care, said in a statement. "At Abbott, we believe that FreeStyle Libre will transform diabetes management, and we're proud to be at the forefront of innovation that empowers people to take control of their health to live their best lives."[3]



Abbott's Freestyle Libre Flash glucose monitoring system received FDA approval after being on the market in 40 countries.

The FDA stressed that people with diabetes must still test their blood sugar regularly; they simply do not need to use a blood test to calibrate the Abbott device. A press release announcing the approval stated, "Risks associated with use of the system may include hypoglycemia or hyperglycemia in cases where information provided by the device is inaccurate and used to make treatment decisions, as well as mild skin irritations around the insertion site.[1]

"It does not provide real-time alerts or alarms in the absence of a user-initiated action; for example, it cannot alert users to low blood glucose levels while they are asleep," the FDA statement continued.

The FDA approved the Abbott device for adults only and the sensor for 10 days[1]; in Europe, the sensor is approved for 14 days.[4] The device is waterproof, and readings are not disrupted if a patient takes acetaminophen. While pricing was not disclosed, the *Chicago Tribune* reported that it is expected to be comparable to the cost of the device in Europe, where the reader and each sensor cost the equivalent of $69.[5]

"Diabetes management requires active participation by the patient. Regular monitoring of glucose levels is especially crucial among patients being treated with insulin," Maria Tulpan, MD, an endocrinologist at Lenox Hill Hospital in New York, New York, said in Abbott's announcement. "What we see with the FreeStyle Libre system is patients gaining a better understanding of the impact of food, exercise, and specific medications on their glucose levels due to availability of the data, which is important in the day-to-day management of diabetes and for behavioral changes towards improved diabetes control."

The FDA's reluctance to approve the Flash CGM system had long frustrated the company and diabetes advocates, who noted that the product was not only in use around the world but also eligible for reimbursement in countries with strict standards, including the United Kingdom and Japan.

The decision came after Abbott published 2 clinical trials involving 50,000 patients, which found that patients who used the scanner frequently had improved glycemic control and less hypoglycemia. ◆

REFERENCES

1. FDA approves first continuous glucose monitoring system for adults not requiring blood sample calibration [press release]. Silver Spring, MD: US Food and Drug Administration; September 27, 2017. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm577890.htm. Accessed September 27, 2017.
2. FDA approval of Dexcom's non-adjunctive indication triggers a new era in diabetes management [press release]. San Diego, CA: Dexcom, Inc; December 20, 2016. www.businesswire.com/news/home/20161220005992/en/FDA-Approval-Dexcom%E2%80%99s-Non-Adjunctive-Indication-Triggers-Era. Accessed October 28, 2017.
3. No more routine finger sticks for Americans with diabetes: Abbott's Freestyle Libre approved in the US [press release]. Abbott Park, IL: Abbott; September 27, 2017. www.prnewswire.com/news-releases/no-more-routine-finger-sticks1-for-americans-with-diabetes-abbotts-freestyle-libre-approved-in-the-us-300527120.html. Accessed September 28, 2017.
4. Brown A, Close K. Abbott's Freestyle Libre transforming glucose monitoring through utter simplicity, fingersticks aside. diaTribe.org. diatribe.org/abbott-freestyle-libre-transforming-glucose-monitoring-through-utter-simplicity-fingersticks. Published January 9, 2015. Accessed October 28, 2017.
5. Schencker L. Abbott diabetes device approved. *Chicago Tribune*. www.chicagotribune.com/business/ct-biz-abbott-diabetes-device-approved-20171001-story.html. Published and accessed September 27, 2017.

Novo Nordisk's Fiasp for Mealtime Use Gains FDA Approval

Christina Mattina

THE FDA HAS APPROVED Novo Nordisk's Fiasp, an insulin aspart injection that can rapidly improve glycemic control at mealtimes for patients with type 1 and type 2 diabetes (T1D and T2D).

According to a statement from the company, the new injection is similar to the fast-acting insulin aspart NovoLog but also contains niacinamide, known as vitamin B_3, which helps the body absorb insulin faster. "According to an analysis in our FDA submission, Fiasp appeared in the bloodstream in 2.5 minutes. In that same analysis, NovoLog appeared in the bloodstream in 5.2 minutes. Due to its fast onset and appearance in the bloodstream, Fiasp can be dosed at the beginning of a mealtime or within 20 minutes after the start of a meal," said Todd Hobbs, MD, chief medical officer of Novo Nordisk in North America, in an email.

Similar to NovoLog, Fiasp will be sold in both 10-mL vials and prefilled delivery pens marketed as FlexTouch by Novo. It will also have an identical list price to NovoLog, and the statement indicates that it will be eligible for the manufacturer's savings card and Patient Assistance Program.

While the original insulin aspart is meant to be fast acting, Fiasp and its niacinamide will help the drug act even more quickly. Speed is especially important during meals, which can lead to blood sugar fluctuations that make it difficult for people with either type of diabetes to achieve optimal blood glucose levels. Fiasp may be used at the start of a meal or within 20 minutes of when the patient begins eating.

The FDA approved Fiasp based on positive results from the Onset clinical trial program, which enrolled more than 2000 adults with T1D or T2D. In phase 2a, patients of both types had a reduction in glycated hemoglobin (A1C) levels after taking Fiasp, whether it was administered at mealtime or after they had started eating. Participants reported some adverse effects, including nasopharyngitis, upper respiratory tract infection, nausea, diarrhea, and back pain. Fiasp is not approved for children.

"With Fiasp, we've built on the insulin aspart molecule to create a new treatment option to help patients meet their postmeal blood sugar target," Bruce Bode, MD, FACE, president of Atlanta Diabetes Associates and an associate professor at Emory University School of Medicine, said in the statement. "The intention of rapid-acting
insulin therapy is to mimic, as much as possible, the natural physiological insulin response that occurs after meals, a process that is important for optimal A1C management." ◆

REFERENCE

Novo Nordisk receives FDA approval for Fiasp, a new fast-acting mealtime insulin [press release]. Plainsboro, NJ: Novo Nordisk; September 29, 2017. press.novonordisk-us.com/2017-09-29-Novo-Nordisk-Receives-FDA-Approval-for-Fiasp-R-a-New-Fast-Acting-Mealtime-Insulin. Accessed October 28, 2017.

Novo Nordisk's Fiasp, a mealtime insulin aspart injection, contains niacinamide for more rapid absorption.

CV Indication Sought for Canagliflozin, Combinations

Mary Caffrey

JANSSEN RESEARCH & DEVELOPMENT has filed a supplemental new drug application with the FDA to add a cardiovascular (CV) indication to canagliflozin, its popular therapy for type 2 diabetes (T2D) sold as Invokana. Company officials announced the application on October 2, 2017.[1]

In the application, Janssen also seeks CV indications for canagliflozin fixed-dose combinations Invokamet and Invokamet XR, the statement said.

The filing was anticipated after a presentation in June at the 77th Scientific Sessions of the American Diabetes Association in San Diego, California, where results of the CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (CANVAS-Renal) studies showed a 14% reduction in the combined primary end point of nonfatal heart attacks, nonfatal strokes, and CV death.[2] Results simultaneously published in the *New England Journal of Medicine* also found that patients taking canagliflozin had a lower risk of hospitalization for heart failure, less loss of kidney function, and a lower risk of progression to albuminuria.[3]

"People with type 2 diabetes have a substantially increased risk of developing cardiovascular disease, and it's encouraging that we now have data to show Invokana may help address this challenge," James F. List, MD, PhD, global therapeutic area head, Cardiovascular and Metabolism, Janssen, said in the company's statement. "Invokana has shown a clear benefit in reducing cardiovascular risk in adults with type 2 diabetes, and we look forward to working with [the] FDA as it reviews our filing."[1]

In March 2013, canagliflozin became the first sodium glucose cotransporter-2 (SGLT2) inhibitor approved to treat T2D.[4] The FDA previously approved a CV indication for empagliflozin, an SGLT2 inhibitor sold as Jardiance by Eli Lilly and Boehringer-Ingelheim.[5] SGLT2 inhibitors have a mechanism of action that involves blocking a protein that normally allows the body to reabsorb glucose; instead, the body discharges excess glucose through the urine, offering people with T2D glycemic control, reduced blood pressure, and modest weight loss.

Another agent approved to treat T2D, the glucagonlike peptide-1 receptor agonist liraglutide, sold by Novo Nordisk as Victoza, received a CV Indication in August 2017 based on results that found it reduced the risk of major CV events by 13%.[6] ◆

REFERENCES

1. Janssen submits supplemental new drug application to US FDA seeking new indication for INVOKANA (canagliflozin) to reduce the risk of major adverse cardiovascular events (MACE) based on landmark CANVAS program [press release]. Raritan, NJ: Johnson & Johnson; October 2, 2017. www.jnj.com/media-center/press-releases/janssen-submits-supplemental-new-drug-application-snda-to-us-fda-seeking-new-indication-for-invokana-canagliflozin-to-reduce-the-risk-of-major-adverse-cardiovascular-events-mace-based-on-landmark-canvas-program. Accessed October 2, 2017.

2. INVOKANA (canagliflozin) significantly reduces the combined risk of cardiovascular death, myocardial infarction, and stroke in the CANVAS program [press release]. Raritan, NJ, and San Diego, CA: Johnson & Johnson; June 12, 2017. www.jnj.com/media-center/press-releases/invokana-canagliflozin-significantly-reduces-the-combined-risk-of-cardiovascular-death-myocardial-infarction-and-stroke-in-the-canvas-program. Accessed October 2, 2017.

3. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377(7):644-657. doi: 10.1056/NEJMoa1611925.

4. US FDA approves INVOKANA (canagliflozin) for the treatment of adults with type 2 diabetes [press release]. Raritan, NJ: Johnson & Johnson; March 29, 2013. www.jnj.com/media-center/press-releases/us-fda-approves-invokana-canagliflozin-for-the-treatment-of-adults-with-type-2-diabetes. Accessed August 21, 2017.

5. US FDA approves Jardiance (empagliflozin) tablets to reduce the risk of cardiovascular death in adults with type 2 diabetes and established cardiovascular disease [press release]. Ingelheim, Germany, and Indianapolis, IN: Boehringer-Ingelheim; December 6, 2016. www.boehringer-ingelheim.com/press-release/fda-approval-jardiance-cv-label. Accessed October 17, 2017.

6. Victoza (liraglutide) is approved in the US as the only type 2 diabetes treatment to reduce the risk of three major adverse cardiovascular events [press release]. Plainsboro, NJ: Novo Nordisk; August 25, 2017. press.novonordisk-us.com/2017-08-25-Victoza-R-liraglutide-is-approved-in-the-US-as-the-only-type-2-diabetes-treatment-indicated-to-reduce-the-risk-of-three-major-adverse-cardiovascular-events. Accessed October 17, 2017.

FDA Updates Afrezza Label; MannKind to Launch New Talks With Payers

EBDM™ *Staff*

ON SEPTEMBER 29, 2017, the FDA granted MannKind Corp a label update for the inhaled mealtime insulin, Afrezza, which CEO Michael Castagna, PharmD, said will let the company set itself apart from rivals for the first time. Castagna said the change will allow a fresh round of conversations with payers about the drug's advantages, including lower rates of hypoglycemia.[1]

The new label, unveiled in an investor call October 2, 2017, states that Afrezza shows up in the bloodstream in approximately 1 minute and reaches its first measurable effects at 12 minutes. More importantly, Castagna pointed to a new table that shows how different doses of Afrezza enter and leave the body quickly, which he said will be crucial in explaining Afrezza's value to doctors and patients.

"This will allow stronger wording with the sales force," Castagna said in an interview with *Evidence-Based Diabetes Management*™ (*EBDM*™), as he discussed plans for MannKind to revamp discussions with doctors about dosing, especially the problem of underdosing. Castagna has said patients sometimes need more units of Afrezza than the number of insulin units they used in an injected form. The FDA, he said, "wants us to be very specific," which he described as "a positive surprise."

The new label also features updated instructions and a new table for titrating the drug, which includes the familiar color-coded insulin cartridges—blue for 4 units of insulin, green for 8 units, and yellow for 12 units—that will help patients new to Afrezza learn what works for them.

Patients who use Afrezza and market watchers who follow MannKind had been waiting to see the language that the FDA would include in the new label to see if it will make a meaningful difference in the way MannKind can position the inhaled insulin with payers and physicians. Afrezza enjoys a loyal core of users who tout its benefits online, and some were urging the FDA to approve an "ultra-fast-acting" designation, which Castagna himself said was a long shot. While the FDA did not add this to the label, Castagna said several key issues were resolved.

Meanwhile, Afrezza will have to compete with Novo Nordisk's faster-acting mealtime insulin, Fiasp, which received FDA approval for patients with type 1 and type 2 diabetes on the same day as the Afrezza label change.[2] Novo Nordisk's chief medical officer for diabetes in North America, Todd Hobbs, MD, said in an e-mail that the FDA's analysis found that Fiasp appeared in the bloodstream in 2.5 minutes.

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Castagna said Afrezza acts even more quickly, but the more clinically relevant issue is how quickly it leaves the body—90 minutes for 4 units, and 3 hours for 12 units.

Afrezza's old label said the drug's onset was comparable with insulin lispro, which made payers skeptical of its value and created barriers to reimbursement. "We have removed the language that restricted our promotional activity," Castagna said during a conference call with analysts.

The Afrezza label update is based on data that MannKind presented at the American Diabetes Association Scientific Sessions in June 2016.[3] "These data articulate the rapid-acting nature of Afrezza to address post-prandial hyperglycemia, setting it apart from other mealtime options available to help patients maintain greater control over their blood glucose levels," said Satish Garg, MD, MBBS, DM, of the Barbara Davis Center for Diabetes at the University of Colorado, in a statement.[1]

The FDA retained the safety warning on Afrezza, which advises that bronchospasms have been observed in certain patients who have asthma or chronic obstructive pulmonary disease. Afrezza is contraindicated in those patients, and the FDA also kept a requirement that patients clear a spirometry test before they gain access to the drug.[4] (The product is delivered through a special inhaler that resembles a whistle.)

It would have been surprising if the FDA altered these requirements, although Castagna said he does hope to address the lung testing requirement in the future. It remains to be seen if this issue is still a barrier for some doctors, now that both Afrezza and Fiasp are approved.

Because Afrezza takes effect within minutes and passes out of the body quickly, advocates for the product say it gives people with diabetes far more flexibility over when they can eat and what foods they can consume, while maintaining glycemic control.[5] But Castagna said endocrinologists have not always appreciated the benefits of rapid-acting insulin and Afrezza's less conspicuous inhaler, which some patients prefer to use in public instead of an injector. Patients have shared stories of difficulty overcoming both physician and payer resistance, in interviews for *EBDM*™.[6]

Afrezza has traveled a bumpy road both before its 2014 approval and beyond. MannKind had a marketing agreement with Sanofi for Afrezza's launch, but that relationship was severed after sales fell far short of expectations. The spirometry requirement was viewed as a barrier because few endocrinologists had this equipment, and many were reluctant to try an inhaled product.

"Payers don't turn overnight on anything. But if you have the label change, and the fact that we can now use a lot of the data that we have, there is clearly a difference between us and other drugs."

—Michael Castagna, PharmD, CEO, MannKind Corp.

The biggest problem in the beginning was formulary access. MannKind leaders pressed forward, and sales have improved in 2017. Castagna's arrival was key. Before coming to MannKind he spent time talking to patients who were enthusiastic Afrezza users, and he became convinced that the product was a hit—the problem involved market barriers, and a need to better train doctors and pharmacists to properly titrate Afrezza.

In a September presentation at the Cantor Fitzgerald Global Healthcare Conference, Castagna said that MannKind would look to produce new data on Afrezza to show that the product was underdosed in early pivotal trials. "I believe if you really dose the product, if you look at some of our modeling data, we believe we can have potentially a superior insulin," Castagna said September 25, according to a Seeking Alpha transcript.[7]

Castagna told *EBDM*™ he anticipates a new agreement with a major pharmacy benefit manager by January 2018, as well as improved access with other payers, although these changes are typically not announced. Castagna has argued for some time that Afrezza is a "completely differentiated" product from competing mealtime insulins and deserves better consideration.

"Payers don't turn overnight on anything," he said. "But if you take the label change, and the fact that we can now use a lot of the data we have, there is clearly a difference between us and other drugs." ◆

REFERENCES

1. FDA updates Afrezza prescribing information [press release]. Westlake Village, CA: Globe Newswire; October 2, 2017. globenewswire.com/news-release/2017/10/02/1138593/0/en/FDA-Updates-Afrezza-Prescribing-Information.html. Accessed October 2, 2017.
2. Novo Nordisk receives FDA approval for Fiasp, a new fast-acting mealtime insulin [press release]. Plainsboro, NJ: Novo Nordisk; September 29, 2017. press.novonordisk-us.com/2017-09-29-Novo-Nordisk-Receives-FDA-Approval-for-Fiasp-R-a-New-Fast-Acting-Mealtime-Insulin. Accessed October 28, 2017.
3. MannKind announces late-breaking data demonstrating faster onset and shorter duration of action compared to mealtime insulins [press release]. New Orleans, LA: Globe Newswire; June 12, 2016. investors.mannkindcorp.com/releasedetail.cfm?ReleaseID=975358. Accessed October 28, 2017.
4. Afrezza website. afrezza.com. Accessed October 28, 2017.
5. Campbell RK. Afrezza: treating diabetes in a physiologic manner. *Am J Manag Care.* 2016;22(SP13):SP473-SP474.
6. Caffrey M. Patients report barriers to getting Afrezza, but A1C results are worth it. *Am J Manag Care.* 2016;22(SP13):SP475-SP476.
7. MannKind's CEO Michael Castagna on Cantor Fitzgerald Global Healthcare Conference (Transcript). Seeking Alpha. seekingalpha.com/article/4109298-mannkinds-mnkd-ceo-michael-castagna-cantor-fitzgerald-global-healthcare-conference-transcript?page=3. Published September 25, 2017. Accessed September 29, 2017.

Intarcia Receives Complete Response Letter From FDA

Mary Caffrey

INTARCIA THERAPEUTICS, INC, maker of a matchstick-size pump that delivers exenatide to treat type 2 diabetes (T2D), announced September 27, 2017, it had received a complete response letter (CRL) from the FDA, asking the company to address manufacturing issues.

A statement said, "The company received clear and constructive guidance from the agency regarding manufacturing aspects of the CRL and is on a clear path to move forward." The company said no additional pivotal trials are anticipated to meet FDA approval requirements but offered no further comment.[1]

Intarcia's ITCA 650, an osmotic mini-pump that delivers continuous microscopic doses of exenatide, outperformed sitagliptin in a 52-week trial,[2] and evidence presented at the most recent meeting of the American Diabetes Association showed patients with T2D were less likely to progress to additional therapy.[3] The treatment method has been seen as a game-changer for populations that struggle with adherence because the mini-pump only has to be replaced once or twice a year.

The company also recently unveiled topline results about the ability of patients to switch from liraglutide, another drug in the class of glucagon-like peptide-1 (GLP-1) receptor agonists. Liraglutide, sold as Victoza by Novo Nordisk, recently received an FDA indication for its cardioprotective benefits based on results of the LEADER trial.[4] (Intarcia has announced that ITCA 650 met the endpoints of its FREEDOM-CVO cardiovascular outcomes trial, but has not presented full results.[5])

According to a statement from Intarcia, the trial showed that patients switching from 1.2 mg or 1.8 mg doses of injectable liraglutide can go directly to a full 6-month dose of the ITCA 650 60 mcg per day osmotic mini-pump. Patients who made the switch showed no statistical differences in safety or tolerability, according to the statement, and glycemic control was stable over 26 weeks after the switch.[6]

Patients making the switch showed a statistically significant reduction in weight, the statement said. The GLP-1 receptor agonist class is known to help patients lose weight, although some experience nausea when they start taking the drug. Intarcia's statement said discontinuation for nausea post-switch was in the 0% to1.5% range.

"These findings support the safety and efficacy profile of ITCA 650 from the FREEDOM clinical development program, and provide important dosing information to assist healthcare providers in clinical decision making," said Michelle Baron, MD, vice president of clinical research and chief medical officer of Intarcia Therapeutics. "We look forward to presenting further details of the study data at a future date."[6] ◆

REFERENCES

1. Intarcia provides corporate update [press release]. Boston, MA: Intarcia Therapeutics; September 27, 2017. intarcia.com/media/press-releases/2017-sep-27-intarcia-provides-corporate-update.html. Accessed October 27, 2017.
2. Rosenstock J, Denham D, Prabhakar R, Azeem R, Kjehms L, Baron M. Superior efficacy of ITCA 650 vs sitagliptin in uncontrolled type 2 diabetes on metformin: the FREEDOM 2 randomized, double-blind, 1-year study. *Diabetes.* 2016;65(suppl 1):183-OR. app.core-apps.com/tristar_ada16/abstract/92b0eac0f984437a5bebc08c57accd16.
3. Caffrey M. Latest results on Intarcia's mini-pump show "clear value to payers," says study author. *Am J Manag Care.* 2017;23(SP11):SP439.
4. Victoza (liraglutide) is approved in the US as the only type 2 diabetes treatment indicated to reduce the risk of three major adverse cardiovascular events [press release]. Plainsboro, NJ: Novo Nordisk; August 25, 2017. press.novonordisk-us.com/2017-08-25-Victoza-R-liraglutide-is-approved-in-the-US-as-the-only-type-2-diabetes-treatment-indicated-to-reduce-the-risk-of-three-major-adverse-cardiovascular-events. Accessed October 28, 2017.
5. Intarcia announces successful cardiovascular safety results in phase 3 FREEDOM-CVO trial for ITCA 650, an investigational therapy for type 2 diabetes [press release]. Boston, MA: Intarcia Therapeutics; May 6, 2016. intarcia.com/media/press-releases/2016-may-6-cardiovascular-safety.html. Accessed October 28, 2017.
6. New Intarcia study evaluates optimal way to switch from daily liraglutide injections to ITCA 650 in patients with type 2 diabetes [press release]. Boston, MA: Intarcia Therapeutics; September 15, 2017. intarcia.com/media/press-releases/2017-sep-15-intarcia-announces-topline-results-from-freedom-3s.html. Accessed October 28, 2017.

FDA Approves Semaglutide, Novo Nordisk's Once-Weekly GLP-1 Receptor Agonist for Type 2 Diabetes

Mary Caffrey

SEMAGLUTIDE, NOVO NORDISK'S once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist for type 2 diabetes (T2D), received FDA approval on December 5, 2017, after beating its rival dulaglutide in a head-to-head trial and coming to the approval process with proof of cardiovascular (CV) benefits in hand. Novo Nordisk announced the approval of the therapy, to be sold as Ozempic, in a statement.[1]

The FDA approved 2 doses of semaglutide, 0.5 mg and 1.0 mg, which will be administered in a prefilled pen. As part of its post-approval requirements, Novo Nordisk will conduct a pediatric trial in adolescents under age 18 and add semaglutide to the 15-year medullary thyroid carcinoma registry being kept for all long-acting GLP-1 therapies.

"We are very excited about the first approval of Ozempic and look forward to making this important innovation available to people in the US with type 2 diabetes in the beginning of 2018," said Mads Krogsgaard Thomsen, executive vice president and chief science officer. "Type 2 diabetes is a complex disease, but with the unique clinical profile of Ozempic, we believe it has the potential to set a new standard for the treatment of the disease."[1]

The approval is based on results from the SUSTAIN clinical research program, which included 8000 patients. The FDA received results from SUSTAIN 6, a 2-year preapproval CV outcomes trial whose results showed a 26% risk reduction in the primary outcome, a composite of nonfatal heart attacks, nonfatal strokes, and CV death.[2] In SUSTAIN 7, semaglutide outperformed the GLP-1, dulaglutide, sold by Eli Lilly as Trulicity, both in lowering glycated hemoglobin (A1C) and resulting in more weight loss.[3]

That 40-week trial compared the 0.5-mg dose of semaglutide with the 0.75-mg dose of dulaglutide and the 1.0-mg dose of semaglutide with the 1.5-mg dose of dulaglutide when added to metformin. From a mean baseline of 8.2% A1C, the lower dose of semaglutide achieved a 1.5% reduction compared with 1.1% for low-dose dulaglutide, and the higher dose of semaglutide achieved a 1.8% reduction compared with 1.4% for the higher dose of dulaglutide.[3]

An FDA panel voted 16-0 to recommend semaglutide for approval on October 18, 2017,[4] after discussing concerns raised in the SUSTAIN 6 trial about increased retinopathy. However, those results did not repeat in SUSTAIN 7, and further analyses suggest those earlier results were due to rapid A1C reduction, not the drug itself.[5]

"So, the goal would be that primary care physicians initiating the first injectable early on in therapy could choose an agent like semaglutide and see the results we've seen—the robust results we've seen—in the SUSTAIN program."

—Todd Hobbs, MD,
Vice President and Chief Medical Officer,
Novo Nordisk

Novo Nordisk has big plans for semaglutide, as it is designing a new round of clinical trials to gain indications for obesity. In addition, results all 10 trials from the PIONEER program, which are examining an oral form of the drug, are expected to be reported in 2018.[6]

Although Novo Nordisk already has a daily GLP-1 on the market with liraglutide (Victoza), the company does not see the 2 as competitors, Todd Hobbs, MD, vice president and chief medical officer, told *Evidence-Based Diabetes Management*™ in an interview. Rather, Hobbs said, the company's research shows that patients with T2D who would benefit from a GLP-1 but have declined to start an injectable drug would be less wary of a once-weekly therapy.

"In our strategy, we agree with others in the industry and with patient groups that GLP-1 agents are underutilized in the treatment of type 2 diabetes. Less than 10% of all diabetes prescriptions are GLP-1 agents," Hobbs said.

"So, the goal would be that primary care physicians initiating the first injectable early on in therapy could choose an agent like semaglutide and see the results that we've seen—the robust results we've seen—in the SUSTAIN program," Hobbs continued. "We're not looking to capture other agent market share as much as we're looking to grow the GLP-1 space that, again, is much underutilized, as GLP-1 agents are underappreciated as excellent agents for type 2 diabetes."

In August, the formulation of liraglutide for T2D, Victoza, received an FDA indication for reducing the risk of CV events, based on results of the LEADER trial.[7] Novo Nordisk also markets a different formulation of liraglutide, called Saxeda, for obesity.

Semaglutide, to be sold as Ozempic, is a GLP-1 receptor agonist.

Hobbs said that semaglutide's weight loss benefits are important in the population that needs GLP-1 therapy, along with the A1C lowering. Depending on the dose, he said, the difference with dulaglutide was between 10 and 15 pounds.

In the interview, Hobbs said early discussions about the clinical results for semaglutide have been positive, "both from thought leaders in the community, but more importantly, payers now are looking at this data and agreeing that this is a very robust agent, with A1C lowering, weight reduction, as well as the lower risk of hypos. They are excited to have this."

Discussions about pricing will not occur until the FDA finalizes the semaglutide label, Hobbs said. "We hope to quickly turn that around…and then slowly and gradually have formulary access in 2018 to support the semaglutide launch." ◆

REFERENCES

1. Ozempic (semaglutide) approved in the US [press release]. Bagsvaerd, Denmark: Globe Newswire; December 5, 2017. https://www.novonordisk.com/media/news-details.2154210.html.
2. Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844. doi: 10.1056/NEJMoa1607141.
3. Semaglutide superior to dulaglutide on glucose control and weight loss in people with type 2 diabetes in SUSTAIN 7 [press release]. Bagsværd, Denmark: Globe Newswire; August 16, 2017. globenewswire.com/news-release/2017/08/16/1086742/0/en/Semaglutide-superior-to-dulaglutide-on-glucose-control-and-weight-loss-in-people-with-type-2-diabetes-in-SUSTAIN-7.html. Accessed December 4, 2017.
4. Semaglutide receives positive 16-0 vote in favour of approval from FDA Advisory Committee [press release]. Bagsværd, Denmark: Globe Newswire; October 18, 2017. novonordisk.com/content/Denmark/HQ/www-novonordisk-com/en_gb/home/media/news-details.2142854.html. Accessed December 4, 2017.
5. Tucker ME. New SUSTAIN 6 data could explain retinopathy worsening. Medscape website. medscape.com/viewarticle/881413. Published June 10, 2017. Accessed December 4, 2017.
6. Highlights to be presented at Novo Nordisk's Capital Markets Day 2017 [press release]. Bagsværd, Denmark: Globe Newswire; November 21, 2017. globenewswire.com/news-release/2017/11/21/1197832/0/en/Highlights-to-be-presented-at-Novo-Nordisk-s-Capital-Markets-Day-2017.html. Accessed December 4, 2017.
7. Mattina C. Liraglutide gains new indication for reducing CV event risk. *The American Journal of Managed Care*. http://www.ajmc.com/newsroom/liraglutide-gains-new-indication-for-reducing-cv-event-risk. Published August 25, 2017. Accessed December 4, 2017.

FDA Approves CV Indication for PCSK9 Inhibitor Evolocumab

EBDM™ *Staff*

THE FDA HAS APPROVED evolocumab (Repatha, Amgen) as the first PCSK9 inhibitor to prevent heart attacks, strokes, and coronary revascularizations in adults with established cardiovascular disease. Amgen announced the approval December 1, 2017, a day ahead of the agency's deadline to act.[1]

The approval is based on results of the FOURIER trial presented in March.[2] The update gives evolocumab an edge over rival alirocumab (Praluent, Sanofi/Regeneron), as sponsors of both proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors work to convince payers their cholesterol-fighting powers are worth a list price of $14,500 a year.[3]

"We are pleased that the FDA made the inclusion of our outcomes data a priority so that patients can benefit from Repatha's ability to reduce life-changing events of heart attacks and strokes," said Sean E. Harper, MD, executive vice president of Research and Development at Amgen. "Despite treatment with current best therapy, many patients are still at high risk for cardiovascular events. Physicians now have a new FDA-approved treatment option to prevent cardiovascular events by dramatically lowering LDL [low-density lipoprotein] cholesterol with Repatha, especially for patients already on maximally-tolerated statin therapy who need further LDL cholesterol lowering."

Evolocumab, sold as Repatha, received a cardiovascular indication based on results of the FOURIER trial.

Evolocumab achieved the new indication through the FDA's priority review process, granted to drugs that treat serious conditions and would offer major improvements in safety or effectiveness over existing options. The agency granted that status in July. FDA also approved evolocumab to be used alongside drugs like statins to treat patients with primary hyperlipidemia.[1]

When PSCK9 inhibitors were approved in 2015, payers set up strict protocols for allowing access to the drug. It remains to be seen whether the label change will improve access to evolocumab for patients.

Results in FOURIER, presented at the American College of Cardiology (ACC) Scientific Sessions, showed evolocumab produced a 15% reduction in the combined primary endpoint of heart attack, stroke, unstable angina, coronary revascularization, or cardiovascular death. As noted in Amgen's statement, these results included the drug's ability to reduce the risk of heart attack by 27%, the risk of stroke by 21%, and the risk of coronary revascularization by 22%.[1,2]

Cardiovascular benefits from evolocumab increased after the first year. However, there was no improvement in cardiovascular death, and payers did not share cardiologists' enthusiasm for the results.[2]

Studies presented at the ACC meeting—and reports from specialists since that time—show that clinicians continue to hit roadblocks when they prescribe PCSK9 inhibitors for patients.[4] "In my experience, it has changed very little. Maybe we have changed a little in terms of our approach to this, possibly some of the payers are little more relaxed," Eliot A. Brinton, MD, FAHA, FNLA, president of the Utah Lipid Center, told *Evidence-Based Diabetes Management*™ in an interview (See **SP564**). With the FOURIER results, he said, "I'm hopeful that this will become less of an issue."

As FOURIER was released, Amgen offered payers a money-back guarantee if patients had a heart attack while taking the drug. The announcement did trigger some contracting agreements with payers, including an early one with Harvard Pilgrim.[5] But others asked whether the arrangement would yield any real savings.[6] A cost-effectiveness analysis published in *JAMA Cardiology* earlier this year found that the current list price of $14,523 "exceeds generally accepted cost-effectiveness thresholds," and that the price would need to fall to $9669 in the United States to achieve the accepted standard of $150,000 per quality-of-life year (QALY). Or, the authors wrote, the drug would need to be targeted to higher-risk populations. (Signers of the analysis included the first 3 authors of listed on the FOURIER trial.)[3]

Last month at the American Heart Association Scientific Sessions, additional analyses from FOURIER showed the drug's effectiveness among 2 groups of very high-risk patients: those with peripheral artery disease, and those with recent or multiple heart attacks and with residual coronary artery disease. Authors of the second study concluded, "These data may permit clinicians to target PCSK9 inhibition to patients who benefit the most."[7]

Big drops in "bad" cholesterol

A monoclonal antibody, evolocumab works to dramatically reduce low-density lipoprotein or "bad" cholesterol by blocking a protein that prevents the liver from carrying cholesterol out of the body. The injectable drug has been shown in clinical trials to reduce LDL cholesterol as much as 60% when patients take it with metformin.[8]

Evolocumab was approved in August 2015, a month after alirocumab. Both were seen as potential blockbusters, but FDA limited labels for both drugs to patients with 2 forms of familial hypercholesterolemia and to high-risk patients with clinical atherosclerotic cardiovascular disease. FDA said that these high-risk cardiovascular patients must use evolocumab alongside maximally tolerated statins.[9]

Prior to approval, an FDA panel declined to recommend evolocumab for broader groups of patients—including the large number who don't tolerate statins well—before seeing cardiovascular outcomes results. ◆

REFERENCES

1. FDA approves Amgen's Repatha (evolocumab) to prevent heart attack and stroke [press release]. Thousand Oaks, CA: Amgen; December 1, 2017. amgen.com/media/news-releases/2017/12/fda-approves-amgens-repatha-evolocumab-to-prevent-heart-attack-and-stroke/. Accessed December 1, 2017.
2. Sabatine MS. Giugliano RP, Keech AC et al, for the FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med.* 2017; 376(18):1713-1722. doi: 10.1056/NEJMoa1615664.
3. Fonarow GC, Keech AC, Pedersen TR et al. Cost-effectiveness of evolocumab therapy for reducing cardiovascular events in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol.* 2017;2(10):1069-1078. doi:10.1001/jamacardio.2017.2762.
4. Caffrey M. Data show it's hard to fill PCSK9 prescriptions, confirming cardiologists' complaints. *The American Journal of Managed Care®*. ajmc.com/conferences/acc-2017/data-show-its-hard-to-fill-pcsk9-prescriptions-confirming-cardiologists-complaints. Published March 19, 2017. Accessed December 1, 2017.
5. Amgen and Harvard Pilgrim agree to first cardiovascular outcomes-based refund contract for Repatha (evolocumab) [press release]. Thousand Oaks, CA: Amgen; May 2, 2017. amgen.com/media/news-releases/2017/05/amgen-and-harvard-pilgrim-agree-to-first-cardiovascular-outcomesbased-refund-contract-for-repatha-evolocumab/. Accessed December 1, 2017.
6. Hernandez I. Revisiting outcomes-based pricing propositions for the PCSK9 inhibitor evolocumab. *JAMA Intern Med.* 2017;177(9):1388-1390. doi:10.1001/jamainternmed.2017.3143.
7. Caffrey M. More FOURIER results highlight evolocumab outcomes among high-risk patients. *The American Journal of Managed Care®*. http://www.ajmc.com/conferences/aha-2017/more-fourier-results-highlight-evolocumab-outcomes-among-higherrisk-patients. Published November 13, 2017. Accessed December 1, 2017.

Eldrin F. Lewis, MD, MPH, on Heart Failure's Place in Diabetes Drug Trials, and the Promise of SGLT2s in Prevention

Mary Caffrey

LEWIS

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inhibitor saxagliptin.[4] The big shock came in September 2015, when the EMPA-REG OUTCOME trial reported that the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin, sold as Jardiance, caused a 38% reduction in CV death.[5] Meanwhile, a secondary endpoint showed a 32% reduction in hospitalization for heart failure among a study population with longstanding diabetes and established CV disease.

Since then, 2 more type 2 diabetes drugs—the SGLT2 inhibitors canagliflozin,[6] sold as Invokana, and the glucagonlike peptide-1 (GLP-1) receptor agonist liraglutide,[7] sold as Victoza—have shown cardioprotective effects; results from CANVAS for canagliflozin showed a 33% risk reduction for hospitalization for heart failure.[6]

As the results generate waves at the FDA and among payers, heart failure is having its moment.

Diabetes specialists appeared at this year's meeting of the American College of Cardiology (ACC) to tout upcoming trials, called EMPEROR HF, that will study empagliflozin in heart failure patients. And Lewis was part of a panel of CV specialists at the American Diabetes Association (ADA) who called for more attention to heart failure, including clinical trials with heart failure as a primary endpoint.

A Prevention Signal?

Separate EMPEROR trials, for EMPagliflozin outcome tRial in Patients With ChrOnic heaRt Failure, will study the SGLT2 inhibitor empagliflozin in patients with preserved and reduced ejection fraction (EF).[8,9] Sponsored by Boehringer Ingelheim and Eli Lilly, the trials are currently recruiting patients and will not be completed before 2020. But a separate trial based on claims data, called CVD-REAL, drew notice at this year's ACC and ADA meetings when results showed the drug class might be able to prevent heart failure in a broad population.[10,11]

Lewis, whose research includes work on preventing disease progression and on patient quality of life, is excited about the possibility that at long last, strategies will be found to prevent heart failure, especially in high-risk patients with diabetes. Attitudes are shifting not only because of trial data but also because payment reform has compelled health systems to think differently about patients with diabetes and heart failure.

"The management of diabetes is a team effort. We have to work with nutritionists; we have to work with psychiatrists, if patients have depression; with endocrinologists; with cardiologists; and with pharmacists to come up with strategies to optimize management of both," he said. "These patients are often depressed because they get frustrated that they can't do a lot of things they want to do. And they want information to try to prevent future adverse events."

What follows are excerpts from the *EBDM*™ interview with Lewis:

***EBDM*™: Why has it taken so long for heart failure among patients with diabetes to receive the attention it's receiving now?**

LEWIS: The main reason that it's taken a while is that the understanding of diabetes and how it relates to cardiovascular disease was that diabetes was a coronary heart disease risk equivalent. That's been considered standard for a long time. As a consequence, I think there's been a lot of emphasis on reducing coronary heart disease—heart attacks, unstable angina, and stroke—kind of an atherosclerotic cardiac event.

Because of that understanding—and we understand the impact of diabetes on the pathophysiology of atherosclerosis—translational research [has focused on] linking the presence of diabetes, or poor glucose control, with atherosclerotic events and models. The focus for patient education, clinical trials, and public health prevention has been on reducing atherosclerotic-related events, or atherosclerotic cardiovascular disease.

What we've noticed in the heart failure community all along is that in almost every predictor that you evaluate for the development of heart failure, diabetes is one of the most important risk factors. In fact, if you take away hypertension, diabetes would probably be the number 2 risk factor for heart failure development.

The reason I think we are seeing attention to heart failure now is 2-fold:

- First, we have 2 trials looking at SGLT2 inhibitors[5,6] [empagliflozin and canagliflozin] that show a reduction in heart failure events in patients with diabetes. So people are saying, "Oh, that's interesting. We need to pay more attention to heart failure."
- Conversely, because there is a single DPP-4 inhibitor agent [saxagliptin] that led to an increased signal of risk for heart failure,[4] there's now concern for the safety of therapies for heart failure in addition to overall atherosclerotic cardiovascular disease.

***EBDM*™: The EMPEROR HF clinical trials are just getting under way. What interests you about these trials?**

LEWIS: The EMPEROR trials are exciting for 2 reasons. First, they are looking at patients with heart failure—both a reduced and a preserved EF population. I don't think you can take data from a high-risk cardiovascular disease trial, such as EMPA-REG and CANVAS, and then extrapolate that to a heart failure population because the heart failure patients have higher risk, and they have other factors that can influence hospitalizations for heart failure. So I think it's interesting and important to look in both the reduced and preserved EF population to examine the use of empagliflozin in this population, to see whether the findings of EMPA-REG and CANVAS can be reproduced in a heart failure population.

The second interesting thing for me is that these trials will be looking at patients without type 2 diabetes. I'm really intrigued to look at the use of this agent in non-diabetes patients. One of the thoughts that I have is: You have a drug that happens to lower glucose, but it has non-glucose-lowering properties that may lead to an improvement of cardiovascular risk. And if that's the case, then we can still use empagliflozin and other SGLT2 inhibitors to treat type 2 diabetes, but we can consider using them in non-diabetes patients as well. The question I would have is, whether the mechanism of action for reduction of cardiovascular risk is glucose related or not, I think it doesn't matter—at the end of the

day, you want to see how people do. You want to reduce the morbidity and mortality associated with the complications of diabetes.

EBDM™: The CVD-REAL trial, while not a randomized clinical trial, suggested there may be potential for SGLT2 inhibitors to be used for prevention. Depending on what we see in the EMPEROR trials, do you see potential for more widespread use of SGLT2 inhibitors—as well as earlier use in the disease life cycle? Is that a possibility?

LEWIS: I think that's a possibility. I give a little pause in terms of applying it generally, but for the moderate- to high-risk population with cardiovascular disease, it looks like there is a benefit. I think the CVD-REAL trial supports the fact that, one, there is early useof SGLT2 inhibitors, and two, it looks like from a large set of payer data that the use of SGLT2 inhibitors—regardless of why—has translated into some improved outcomes in the real world. I'm encouraged by that, and I actually see that we'll be using more SGLT2 inhibitors fairly rapidly.

EBDM™: Has the payment reform movement—and particularly the focus on hospital readmissions—caused health systems to pay more attention to heart failure, given the high rate of readmissions and the costs associated with this condition?

LEWIS: I think so. In general, heart failure patients are complicated. The mean age of patients is in the early 70s, and so there may not be as much interest in general in the typical heart failure patient, unfortunately. The older heart failure patients come with a lot of comorbid illnesses—chronic kidney disease, COPD [chronic obstructive pulmonary disease], hypertension, end-stage renal disease—multisystem organ failure. They have frailty, sarcopenia, etc. When these patients come in, they are complicated, and sometimes we cannot dramatically improve them. They are expensive for the hospital system because of the comorbid conditions. As a consequence, there hasn't been as much focus from mainstream cardiology on heart failure management. We traditionally had readmission rates within 30 days of higher than 30%, with the thinking, "These are complicated patients, and you can't reduce it."

When third-party payers started saying there will be a penalty associated with 30-day all-cause readmission, all of a sudden there's an interest in the hospital systems' coming up with strategies to reduce readmissions.

With ACOs [accountable care organizations], where everyone must share in coming up with efficiency measures, that alone has incentivized hospital systems to come up with strategies to prevent hospitalizations for heart failure. And the negative incentives from third-party payers to prevent readmissions will also offer a reason to provide necessary resources to prevent readmissions.

What we've noticed since a lot of these changes have occurred is that you have seen a reduction in readmissions—down to the 24% range instead of well over 30%. And we're starting to better understand why these patients are hospitalized in the first place.

EBDM™: Preventing disease progression and hospital admissions is the goal. But we hear that when physicians try to start patients on newer therapies, such as SGLT2 inhibitors, earlier in the life cycle of the disease, payers often say no. How can we address these challenges going forward?

LEWIS: There will be challenges—payer restrictions are problematic. The tricky part is, it's hard to know whether we're receiving them early enough because we don't have enough trials to inform us about the timing and the impact of the tiered approach. Metformin still becomes the foundation of diabetes management. Most primary care physicians and endocrinologists would start metformin first. There hasn't been a head-to-head trial that asks, "In newly diagnosed diabetes, should we start metformin or an SGLT2 inhibitor?" Once we have that information, it will be easier to go away from the current guidelines. The guidelines say, "Start with metformin and then expand."

In terms of restrictions—and I don't have data, this is strictly my opinion—if you have a prior authorization that is required, a busy clinician will often find that hurdle somewhat challenging. You have to slow down, complete the form, and sometimes have to do a peer-to-peer review, which takes additional time. If you're a busy clinician, it becomes challenging in between seeing your 45 to 50 patients. Prior authorization can be enough of a hurdle to reduce utilization.

Unfortunately, we don't have primary data that evaluate primary care clinicians on why they haven't started a new therapy. Say you have patient A, who clearly qualifies for initiating an SGLT2 inhibitor; their A1C [glycated hemoglobin] is uncontrolled. And the clinician chooses not to [prescribe the drug]. The question is to go back to the provider and ask, "Why didn't you do it?" That kind of information would be very helpful. Sometimes it's lack of knowledge; sometimes it's the hurdle.

In terms of the knowledge, the other tricky part is, who manages the diabetes? Diabetes and heart failure can both be managed by a specialist; you can have an endocrinologist managing diabetes, a cardiologist or heart specialist managing the heart failure. But in the real world, about 80% of heart failure patients are managed by their primary care doctor. For diabetes, I would assume it would be a relatively high number as well. If you're a primary care doctor who has 15 minutes to deal with all the problems that a patient has, in addition to diabetes and heart failure, it becomes challenging to not only have the knowledge gap reduced, so that they understand: This is a drug that can be used to treat diabetes, and here's a novel drug to treat heart failure. But they have to understand when you would use an SGLT2 inhibitor, versus a DPP-4 inhibitor, versus a GLP-1 receptor agonist, versus using insulin initially. So, these algorithms can be complex, and for heart failure, it's even more complex.

I think the future of diabetes and heart failure management rests with electronic health records [EHRs] with logic built in—to help trigger the primary care doctor to identify patients who might benefit from some of these more novel therapies. Once a new guideline comes out, you build that into the EHR decision-making process.

EBDM™: Are we doing enough to prevent heart failure in patients with diabetes? Do we need to do more?

LEWIS: Given that diabetes is the number 2 risk factor for heart failure, we have to. Especially in patients who have what I call the trifecta—hypertension, diabetes, and preexisting atherosclerotic cardiovascular disease—those are very high-risk populations. Lipid lowering is important, as well, in these patients, but we need some type of precision medicine approach to managing the prevention of heart failure. If you look at the natural history of patients after they develop heart failure, you're looking at a median survival of 5 years; at best, the median survival is 8 years, if we include the asymptomatic patients.

We should absolutely come up with strategies to prevent heart failure—and that's what excites me about the SGLT2 inhibitors. I'm waiting to see the additional trials come out to add to our understanding, but the fact that we have 2 trials that have reduced not only mortality but also reduced heart failure is very important. ◆

REFERENCES

1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes [published correction appears in *N Engl J Med.* 2007;357(1):100]. *N Engl J Med.* 2007;356(24):2457-2471. doi: 10.1056/NEJMoa072761.

2. FDA guidance for industry. Diabetes mellitus: Developing drugs and therapeutic biologicals for treatment and prevention. US Food and Drug Administration. fda.gov/downloads/Drugs/.../Guidances/ucm071624.pdf. February 2008, Draft. Accessed October 15, 2017.

3. Caffrey M, Szwed A. Heart failure needs more attention in diabetes drug trials, expert says. *The American Journal of Managed Care®*. www.ajmc.com/conferences/ada-2017/Heart-Failure-Needs-More-Attention-in-Diabetes-Drug-Trials-Expert-Says. Published June 11, 2017. Accessed October 15, 2017.

4. Scirica BM, Bhatt DL, Braunwald E, et al, for the SAVOR-TIMI 53 Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* 2013;369(14):1317-1326. doi: 10.1056/NEJMoa1307684.

5. Zinman B, Wanner C, Lachin JM, et al, for the EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128. doi: 10.1056/NEJMoa1504720.

6. Neal B, Perkovic V, Mahaffey KW, et al, for the CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017; 377(7):644-657. doi: 10.1056/NEJMoa1611925.

7. Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375(4):311-322. doi: 10.1056/NEJMoa1603827.

8. EMPagliflozin outcomE tRial in Patients With chrOnic HeaRt Failure With Reduced Ejection Fraction) EMPEROR-Reduced. www.clinicaltrials.gov/ct2/show/NCT03057977. Updated October 4, 2017. Accessed October 15, 2017.

9. EMPagliflozin outcomE tRial in Patients With chrOnic HeaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved). www.clinicaltrials.gov/ct2/show/NCT03057951. Updated October 4, 2017. Accessed October 15, 2017.

10. Caffrey M. Can SGLT2 inhibitors prevent heart failure in a broad population? *The American Journal of Managed Care®*. www.ajmc.com/conferences/acc-2017/can-sglt2-inhibitors-prevent-heart-failure-in-a-broad-population-results-from-a-real-world-study. Published March 19, 2017. Accessed October 15, 2017.

11. Kosiborod M, Cavender MA, Fu AZ, et al; CVD-REAL Investigators and Study Group. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study. *Circulation.* 2017;136(3):249-259. doi: 10.1161/CIRCULATIONAHA.117.029190.

"Sprint to Zero": A Strategy to Address High Rates of Nontraumatic Amputations in Minority Communities

Jeffrey Carr, MD, FACC, FSCAI

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The good news is that we already have the capability to identify and treat vascular diseases before they progress to the point of amputation. And we have the technical know-how to bring the right care to the right people. What's missing is a comprehensive, national strategy that integrates public awareness, increased screening and arterial testing for those determined to be at risk, and improved multidisciplinary care with new patient safety measures.

Increased Awareness

With as many as 18 million Americans at risk for limb loss due to peripheral artery disease (PAD)[6] and the unprecedented prevalence of diabetes, we clearly need more effective public awareness.[2] This applies to patients, who should receive better education about the risks of PAD, as well as providers, who should have better incentives to perform standard arterial testing on at-risk patients. In this regard, CMS should take cues from the previously successful Fistula First Breakthrough Initiative, which significantly increased the percentage of patients with end-stage renal disease receiving fistulas by setting standards for the entire field.[7] Implementing a similar amputation reduction initiative, with a specific focus on providers in minority communities, could raise the benchmark across the whole spectrum of cardiovascular care providers.

As many as 18 million Americans are at risk of limb loss due to peripheral artery disease. Members of minority groups face a disproportionate level of risk.

Screening for At-Risk Populations

Based on the US Preventive Services Task Force assigned grade of I, or insufficient evidence, there is great room for improvement in PAD screening the general US population and in identifying disease in asymptomatic, at-risk populations. Despite guidelines issued by the American College of Cardiology and American Heart Association that recommend screening of at-risk patients—those who are over age 65, have a history of diabetes, smoking, and/or PAD, or have received a diagnosis of other vascular disease[8]—we know that screenings are not taking place among these patient groups, therefore increasing the likelihood for advanced disease and limb loss.

We have the capability to identify and treat vascular diseases before they progress to the point of amputation. We have the technical know-how to bring the right care to the right people. What's missing is a comprehensive, national strategy that integrates public awareness, increased screening, and arterial testing for those determined to be at risk and improved multidisciplinary care.

No Amputation Without Arterial Testing

But awareness is not enough if arterial testing remains underutilized. According to a 2014 study, more than 30% of patients who underwent a nontraumatic amputation had no arterial testing the prior year to evaluate whether they would be a potential candidate for revascularization or another intervention.[9] Providers should make screening mandatory for all at-risk patients, and no amputation should occur unless a patient receives an invasive angiogram or other arterial vascular evaluation first. A 2011 analysis of more than a million Medicare patients with critical limb ischemia (CLI) found that this practice reduced the odds of amputation among patients with CLI by 90%.[10] At some centers—particularly The Surgical Clinic in Nashville, Tennessee, and Martin Memorial Hospital in Stuart, Florida—an angiogram before an amputation is routine. Both centers saw significant declines in their nontraumatic amputation rates since implementing this requirement.[11,12]

Improved Quality Measures and Multidisciplinary Care

Many facilities remain out of reach for patients living in underserved communities, which have populations that are disproportionately African American, Hispanic, and Native American. Reaching these communities requires that care be improved in

other settings and that CMS promote policies to encourage more providers to coordinate care.

Quality measures for facilities that accept Medicare are also improving. As recently as this year, CMS approved 2 new cardiovascular-related measures as Qualified Clinical Data Registries (QCDRs), which will track the rates of noninvasive vascular testing prior to revascularization for patients with CLI or who have claudication. Because they are applicable to all specialties that provide revascularization care, these measures are expected to give investigators greater insight into the decision-making process that precedes an amputation.

However, there is room for CMS to go further. The CardioVascular Coalition's most recent Quality Measures Working Group recommends that CMS implement an additional measure to track use of a patient safety survey prior to undergoing a nontraumatic amputation. Facilities would be required to go through a Safe Surgery Checklist with patients before proceeding with an amputation and report the results as part of Medicare's QCDR program.

Better measures like these have the potential to improve care quality and save money. Research shows that patients who avoid amputation have a higher quality of life afterward and experience fewer adverse effects associated with limb loss—such as depression and disability.[13] And, according to an analysis by Avalere Health, cutting the number of Medicare patients with major amputations in half could save the program $2 billion over 10 years.[14]

When considering all these factors, it is clear that opportunities exist for improving how both PAD and CLI are screened, diagnosed, and treated among the Medicare population, particularly minorities who are at greatest risk. The progress made in the field of vascular care indicates that there is no good reason any amputation should occur when limb preservation is a possibility. This is why the CardioVascular Coalition is calling for a national Sprint to Zero initiative that seeks to eliminate senseless amputations through increased awareness, higher screening rates, and the use of a multidisciplinary approach that will ensure no amputation is performed on a patient without arterial testing. ◆

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REFERENCES

1. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the Prevalence of Limb Loss in the United States: 2005 to 2050. *Arch Phys Med Rehabil.* 2008;89(3):422-429. doi: 10.1016/j.apmr.2007.11.005.

2. Centers for Disease Control and Prevention. National diabetes statistics report, 2017. https://cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Published July 17, 2017. Accessed November 9, 2017.

3. Goodney PP, Dzebisashvili N, Goodman DC, Bronner KK; Dartmouth Atlas of Health Care. Variation in the care of surgical conditions: diabetes and peripheral arterial disease. www.dartmouthatlas.org/downloads/reports/Diabetes_report_10_14_14.pdf. Published October 2014. Accessed November 9, 2017.

4. Mustapa J, Fisher BT, Rizzo JA, et al. Racial disparities in amputation rates for the treatment of peripheral artery disease (PAD) using the healthcare cost and utilization project (HCUP) database. Presented at: ISPOR 21st Annual International Meeting; May 21-25, 2016; Washington, DC. cardiovascularcoalition.com/wp-content/uploads/2016/11/CSI-Racial-Disparities-African-Americans-Hispanics-ISPOR-POSTER-2016.pdf. Accessed November 9, 2017.

5. Rizzo, JA, Chen J, Laurich C, et al. Racial disparities in amputation rates among Native Americans with peripheral artery disease: analysis of the health care cost and utilization project database (HCUP). *Value in Health.* 2016;19(3):55. doi: 10.1016/j.jval.2016.03.140.

6. Aggarwal S, Loomba RS, Arora R. Preventive aspects in peripheral artery disease. *Ther Adv Cardiovasc Dis.* 2012;6(2):53-70. doi: 10.1177/1753944712437359.

7. Fistula First Catheter Last. ESRD NCC website. esrdncc.org/en/fistula-first-catheter-last. Accessed November 26, 2017.

8. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol.* 2017;69(11):1465-508. doi: 10.1016/j.jacc.2016.11.008.

9. Vemulapalli S, Greiner MA, Jones WS, Patel MR, Hernandez AF, Curtis LH. Peripheral arterial testing before lower extremity amputation among Medicare beneficiaries, 2000 to 2010. *Circ Cardiovasc Qual Outcomes.* 2014;7(1):142-150. doi:10.1161/CIRCOUTCOMES.113.000376.

10. Henry AJ, Hevelone ND, Belkin M, Nguyen LL. Socioeconomic and hospital-related predictors of amputation for critical limb ischemia. *J Vasc Surg.* 2011;53(2):330-339.e1. doi: 10.1016/j.jvs.2010.08.077.

11. Fisher BT, Hannan S, Martinsen BJ. Team-based approach for the treatment of arterial wounds reduces amputation rates in critical limb ischemia patients. *JACC: Cardiovasc Intervent.* 2016;9(4):S34-S35. doi: doi.org/10.1016/j.jcin.2015.12.155.

12. Sanguily J, Martinsen BJ, Igyarto Z, Pham MT. Reducing amputation rates in critical limb ischemia patients via a limb salvage program: a retrospective analysis. *Vasc Dis Manag.* 2016;13(5):E112-E119.

13. Yost M. Cost-benefit analysis of critical limb ischemia in the era of the ACA. *Endovascular Today.* evtoday.com/2014/05/cost-benefit-analysis-of-critical-limb-ischemia-in-the-era-of-the-affordable-care-act. Published May 2014. Accessed November 9, 2017.

14. Avalere Health, May 2015 analysis of CY2011-CY2013 Medicare claims. Data on file.

PAYER PERSPECTIVE

Moving Pharma Contracting Into the Era of Accountability

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GRAF

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clinical outcomes, and cost; differences in spending can be 10-fold or greater.[2] Given that we are paying a significant premium for healthcare relative to other industrialized nations, there should be a more consistently excellent product.[3] So, as healthcare providers and healthcare payers are under intense scrutiny to reliably deliver measurably better health, they are looking to all elements of the health supply chain to deliver that value.

At the same time, the cost to bring a therapy through the FDA-approval process keeps rising, and pressure from generics and alternative medications is growing. Increased sophistication of the mechanisms of action of these new drugs, along with expectations from venture capital firms and shareholders, has pushed the overall cost of pharmaceuticals past what we spend on physicians in the United States. Today, pharmaceutical spending is second only to the spend on hospitals.[4] This has led to potential innovation in the pricing and positioning of new million-dollar therapies, as the drive to deliver true value for patients/plan members intensifies.[5]

For many years, payersand, to some extent, providers have been shifting from traditional fee-for-service care toward models that reward results. Tentative steps such as paying for process metric achievement for primary care physicians to more quality gated gainsharing models have given way to far more performance risk sharing, where providers are focused on total medical expense budgets or partial capitation agreements. Some states, such as California and Maryland, have even more advanced models. Despite these advances, the share of healthcare spending tied to these new models remains small and the pressure to develop ways to drive quality improvement as a cost-saving measure continues to mount.[6] Additionally, as new and very expensive therapies are developed, the desire to ensure efficacy at these prices is even greater. The need to show that a medication can change a disease trajectory and affect an outcome that patients, providers, payers, and employers (or whoever the ultimate payers is) care about is paramount.

This begs the question: what does each group care about? The simple answer is that each stakeholder cares about many things and many concerns overlap[7]:

- **Patients** care about the impact on their lives and functional status. They care what a drug costs them out of pocket, and they care somewhat about the overall cost.
- **Employers** have similar concerns, but they focus more on cost than individual responsibility.
- **Providers** care about tho same outcomes as patients and employers, but with a greater focus on medical quality in addition to impact, and are interested in intermediate outcome measures far more than patients.
- **Payers** care about medical quality and increasingly about total cost, but they also worry about the customer service experience of members and how drug costs affect employers.[8]

The other important consideration is the time horizon of the impact. For patients, it is their lifetime; for employers, the duration of employment; for payers, the period of coverage; and for providers, the length of time they spend caring for each patient. These different time horizons create additional challenges in thinking through how to create a successful value equation.[9] The ideal is a program that improves medical quality in a way that is visible and important to patients and lowers the total cost of care in a year or less (for Medicaid, perhaps in a month or less). This is very hard to create. Readmission reductions programs are a great example: They have a big impact and quickly and definitively impact cost. Medical quality is often more about the reliable delivery of the best care.[10]

The cost to bring a therapy through the FDA-approval process keeps rising, and pressure from generics and alternative medications is growing. Increased sophistication of the mechanisms of action of these new drugs, along with expectations from venture capital firms and shareholders, has pushed the overall cost of pharmaceuticals past what we spend on physicians in the United States. Today, pharmaceutical spending is second only to spend on hospitals.

This creates a real challenge for pharma. While most drugs take considerable time to affect outcomes that matter to patients and translate into cost reductions, the impact on medical quality may come quickly. In diabetes, for example, although many medications have been shown to reduce glycated hemoglobin levels within several months, which makes doctors happy, they take far longer to impact heart attack rates, which is a measure that patients can appreciate. Insurers, meanwhile, often don't see value until an avoided heart attack translates into lower costs for patients—who are not admitted for the heart attacks they don't have. And the employer won't see the impact until enough employees avoid heart attacks to actually bring down future rate increases. This is a significant issue now that some drugs cost hundreds, thousands, or tens of thousands of dollars per month.

For patients with diabetes, thus far, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, evolocumab (Repatha) has been shown to reduce cardiovascular (CV) events (eg, hospitalization, heart attack and stroke), which is an incredibly important outcome for a patient. This happens in a clinically relevant time horizon (median 26 months), which is important for patients and their employers and from a public policy standpoint. Politicians have chosen to weigh in on mandating coverage of even marginally effective treatments (Ornish intensive cardiac rehab for Medicare for instance) and a case could be made that the evidence is powerful. However, insurers will be challenged by creating appropriate rules so that this medication is used only

for those patients who will truly benefitbecause of implementation issues.[11] Clearly, reducing CV events will be important for both quality and cost. However, since many patients are currently well treated with much less expensive medications, and many more could be if they were maximally managed, there is a risk that patients will receive these $14,000-per-year drugs when they really do not need them.[12] If patients are exposed to side effects and complications of PCSK9 inhibitors, this would impact the cost savings they create. Additionally, all cause morbidities and mortality and cost need to be considered. Reducing CV complications alone is not enough.

An analysis of the total medical expense would be helpful and key to the real value equation. Understanding the quality improvements, both on CV outcomes and overall health, is the first step. We need to know mortality impact, morbidity impact, and utilization impact to measure the positive effects. We also need to know the full cost, not just of the medication, but of managing the complications, the natural course of progression, and the cost of monitoring. From an employer and patient perspective, the lost work time and other "life" effects are very important but largely invisible to the insurer and to the physician.

There's also the challenge of defining a realistic comparator. Total medical expense, a likely best candidate, is often harder to determine than it would first appear—and absent a solid comparator—the relative impact is impossible to judge. Pharma has offered several interesting ideas for how this might be managed:

- **The challenge of rebates.** We are now well past the era of using volume discounts to help control costs. The goal today is controlling the total cost of care, especially pharmaceutical costs, which have outpaced the overall medical spend. Some have looked at rebates or refunds if certain complications occur, such as heart attacks.[13] The challenge is that these practices do not necessarily support the optimal use of the medication, that they encourage widespread marketing to the lowest-risk patients to ensure complications do not occur too frequently. This also does not get at the underlying issue: the therapy may simply cost too much. Offering a 30% reduction for certain patients on a drug that is 50% overvalued does not control costs.

- **Pay-for-performance.** The idea of not charging patients who do not respond to a treatment is another approach. This model is uniquely suited to the high-cost specific-use medications being introduced in cancer care; it would fail for other drug classes where determining response is more difficult. To truly develop comprehensive accountability, a program that includes annual total cost of care and trend impact is needed. The challenge here is that there are many factors outside of a specific disease and certainly beyond a drug's impact that affect the total cost of care. Many pharmaceutical companies have developed or partnered with others to provide wrap-around services to improve adherence and modify lifestyle—offering stress reduction treatments or help with exercise and diet to support improved outcomes and reduced healthcare utilization. However, these services may interfere with similar programs at the health plan or provider level. Also, these programs are either not explicitly tied to cost or only focus on the cost of the specific diagnosis or disease state. This makes perfect sense from a pharmaceutical and provider perspective. However, from the payer, employer, and patient perspectives, programs that reduce CV costs and utilization but raise costs in other areas are not helpful. Proving causality or even an indirect relationship between the two is even harder.

- **Making partnerships scalable.** For this approach, a collaboration between physicians, other providers, and drug manufacturers would help with the all-encompassing nature of total medical expenses. However, this only becomes practical for companies that have medications for multiple disease states and systems that have large numbers of patients. For insurers, this works only if the same pharma–provider coalitions care for a significant number of their members. The practical application of these global innovations is challenging.

What can we really do? How can we move forward? It is clear that there is no silver bullet to improving quality while driving down cost in healthcare; in the pharmaceutical arena, as well. A tailored approach blending all the ideas will be necessary. We also need to look for related areas in which we can eliminate non–value-added costs from the system. Examples include site-of-service issues, where the infusion location often translates into a 2- to 10-fold cost difference, or cost-plus-percentage markups for medications that work well when medications are priced in the hundreds of dollars but fail when prices reach $500,000. These are simple changes that can impact cost that do not really create accountability but do rationalize the overall pharmaceutical spend.

Creating a direct link between the impact of the proper use of the medication and the corresponding price paid is critical to the long-term success of healthcare. The keys are:

1. Reaching agreement among payers, providers, and pharma on a process for measuring the direct and long-term impacts, quality, utilization, and cost of new therapies.
2. Agreeing on a process to ensure selection of the optimal patients for each new therapy, along with a mechanism to create accountability for patient selection.

For many, the idea of a rebate for treatment failures or complications makes sense; for others, the idea of overall cost of care for a specific disease category on an annual basis works; for still others, nonpayment is ideal if a patient does not respond. By working through these areas and tailoring the methodology to the disease state and specific medication profile, we can best make lasting progress to drive quality improvement to reduce total cost of care rather than just cutting a few dollars today. ◆

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REFERENCES

1. National Health Expenditure fact sheet. Centers for Medicare & Medicaid Services website. cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nhe-fact-sheet.html. Updated June 14, 2017. Accessed November 24, 2017.

2. Pritchard D, Petrilla A, Hallinan S, Taylor DH, Schabert VF, Dubois RW. What contributes most to high healthcare costs? Healthcare spending in high resource patients. *J Manag Care Spec Pharm.* 2016;22(2):102-109. doi: 10.18553/jmcp.2016.22.2.102.

3. Squires D, Anderson C. *US health care from a global perspective: spending, use of services, prices, and health in 13 countries.* The Commonwealth Fund website. commonwealthfund.org/publications/issue-briefs/2015/oct/us-health-care-from-a-global-perspective. Published October 8, 2015. Accessed October 16, 2017.

4. Glied S, Ma S, Solís-Román C. Where the money goes: the evolving expenses of the US health care system. *Health Aff (Millwood).* 2016;35(7):1197-1203. doi: 10.1377/hlthaff.2015.1356.

5. Keshavan M. We may soon have our first $1 million drug. Who will pay for it? And how? *STAT.* October 13, 2017. statnews.com/2017/10/13/gene-therapy-pricing/. Accessed November 24, 2017.

6. Blumenthal D, Abrams MK. Tailoring complex care management for high-need, high-cost patients. *JAMA.* 2016;316(16):1657-1658. doi: 10.1001/jama.2016.12388.

7. Davidson SM, Shwartz M, Stafford RS. The feasibility and value of new measures showing patterns of quality for patients with three chronic conditions. *J Ambul Care Manage.* 2008;31(1):37-51. doi: 10.1097/01.JAC.0000304096.59205.e0.

8. Blumenthal D. Value-based drug pricing: watch out for side effects. The Commonwealth Fund website. commonwealthfund.org/publications/blog/2016/jul/value-based-drug-pricing. Published July 21, 2016. Accessed October 16, 2017.

9. Silow-Carroll S, Alteras T. Value-driven health care purchasing: four states that are ahead of the curve. The Commonwealth Fund website. commonwealthfund.org/publications/fund-reports/2007/aug/value-driven-health-care-purchasing--four-states-that-are-ahead-of-the-curve. Published August 1, 2007. Accessed October 16, 2017.

10. Mittler JN, O'Hora JL, Harvey JB, Press MJ, Volpp KG, Scanlon DP. Turning readmission reduction policies into results: some lessons from a multistate initiative to reduce readmissions. *Popul Health Manag.* 2013;16(4):255-260. doi: 10.1089/pop.2012.0087.

11. Sabatine MS, Giugliano RP, Keech AC, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med.* 2017;376(18):1713-1722. doi: 10.1056/NEJMoa1615664.

12. Hernandez I. Outcomes-based pricing for PCSK9 inhibitors. *Am J Manag Care.* ajmc.com/contributor/inmaculada-hernandez-pharmd/2017/09/outcomes-based-pricing-for-pcsk9-inhibitors. Published September 24, 2017. Accessed November 24, 2017.

13. Carroll J. Heart attack while on Repatha? Amgen will give you your money back. *Endpoints News.* March 20, 2017. endpts.com/heart-attack-while-on-repatha-amgen-will-give-you-your-money-back/. Accessed November 24, 2017.

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