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Volume 21
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# Evidence-Based Diabetes Management

## THE OBESITY ISSUE

*Research Report*

## Joslin's Hamdy: *Evidence Shows Diet, Exercise Effective Against Diabetes, Obesity Long-Term*

ANDREW SMITH

Osama Hamdy, MD, PhD, has spent much of the past few years presenting study data that dispute conventional wisdom about the futility of diet and exercise and suggest that lifestyle intervention may be the key to fighting type 2 diabetes mellitus (T2DM).

Each year, he reports another 12 months of follow-up information on 129 patients who spent 12 weeks in the Weight Achievement and Intensive Treatment (Why WAIT) program, based at the Joslin Diabetes Center. Each year, the information indicates that a majority of patients have maintained significant weight loss and enjoyed significant health benefits.[1,2] Each year, audiences tell Hamdy that the results are extremely promising but too preliminary to justify any major shift in treatment paradigm.

There are some indications that things may change this year, with the publication of a full 5 years of follow-up data. The study abstract that Hamdy and his colleagues prepared for the annual meeting of the American Diabetes Association (ADA) in June generated only moderate coverage in the specialty press, but it did win the Michaela Modan Memorial Award for its contribution to the understanding of T2DM,[3] and Hamdy hopes that many researchers and clinicians will come to appreciate the significance of its findings. (Medscape included the study among

(continued on page SP453)

*Commentary*

## Stumbling Toward Access to Evidence-Based Care for the Chronic Disease of Obesity

THEODORE K. KYLE, RPH, MBA; AND FATIMA CODY STANFORD, MD, MPH, MPA

One of the most substantial medical and financial threats to American healthcare is untreated obesity. Although options and guidelines for pharmacotherapy are growing, access to care is falling behind advances in treatment.

### A COMPLEX, CHRONIC, AND COSTLY DISEASE

Obesity is a complex, chronic, and costly disease that has been shown to be the key driver behind 4 of the 10 most deadly and expensive diseases worldwide—ischemic heart disease, stroke, hypertension, and diabetes. More than one-fourth of total healthcare expenses in the United States are attributable to the rise in the prevalence of excess weight and obesity.[1] Obesity has been characterized as the greatest threat to American health for this century,[2] and it is rapidly becoming apparent that obesity will soon undermine the affordability of American healthcare, due to the epidemic of chronic diseases it is causing.[3]

In 2013, the American Medical Association (AMA) joined with the National Institutes of Health, the Obesity Society, the American Association of Clinical Endocrinologists, and the Endocrine Society in recognizing obesity as a complex chronic disease that requires a range of interventions for treatment and prevention.[4] Because of the symbolic significance of this decision,

(continued on page SP455)

*Pharmacy Management*

## For Now, PBMs Just Say No to High-Cost PCSK9 Inhibitors

MARY K. CAFFREY

When the FDA approved the first 2 PCSK9 inhibitors this summer, there was plenty of attention from health plans and cardiologists alike to scope of the labels, especially relative to what European regulators allowed for these breakthrough cholesterol drugs. But when the approvals came down for alirocumab (Praluent) on July 24, 2015, and for evolocumab (Repatha) on August 27, 2015, the next question was: what will they cost?[1-3]

First, Sanofi-Regeneron set the price of alirocumab at $14,600 a year for both the 75-mg and 150-mg injections—a eye-popping $40 a day.[4] Then, despite speculation that Amgen might price evolocumab well below its competitor, the second drug came in at $14,100 a year for its 140-mg injection.[5] Both drugs are given twice a month, although evolocumab plans to have a 420-mg monthly dose available next year.

The first entrants in this long-awaited class of monoclonal antibodies, which reduced low-density lipoprotein (LDL) cholesterol up to 60% in clinical trials, arrived well above the $7000 to $12,000 annual cost that analysts predicted.[6] ExpressScripts, the nation's largest pharmacy benefits manager (PBM), and CVS Health, the second-largest, had spent months before the FDA actions making it clear they intended to leverage the presence of 2 drugs to demand savings for their clients, and ultimately, consumers.[6-8]

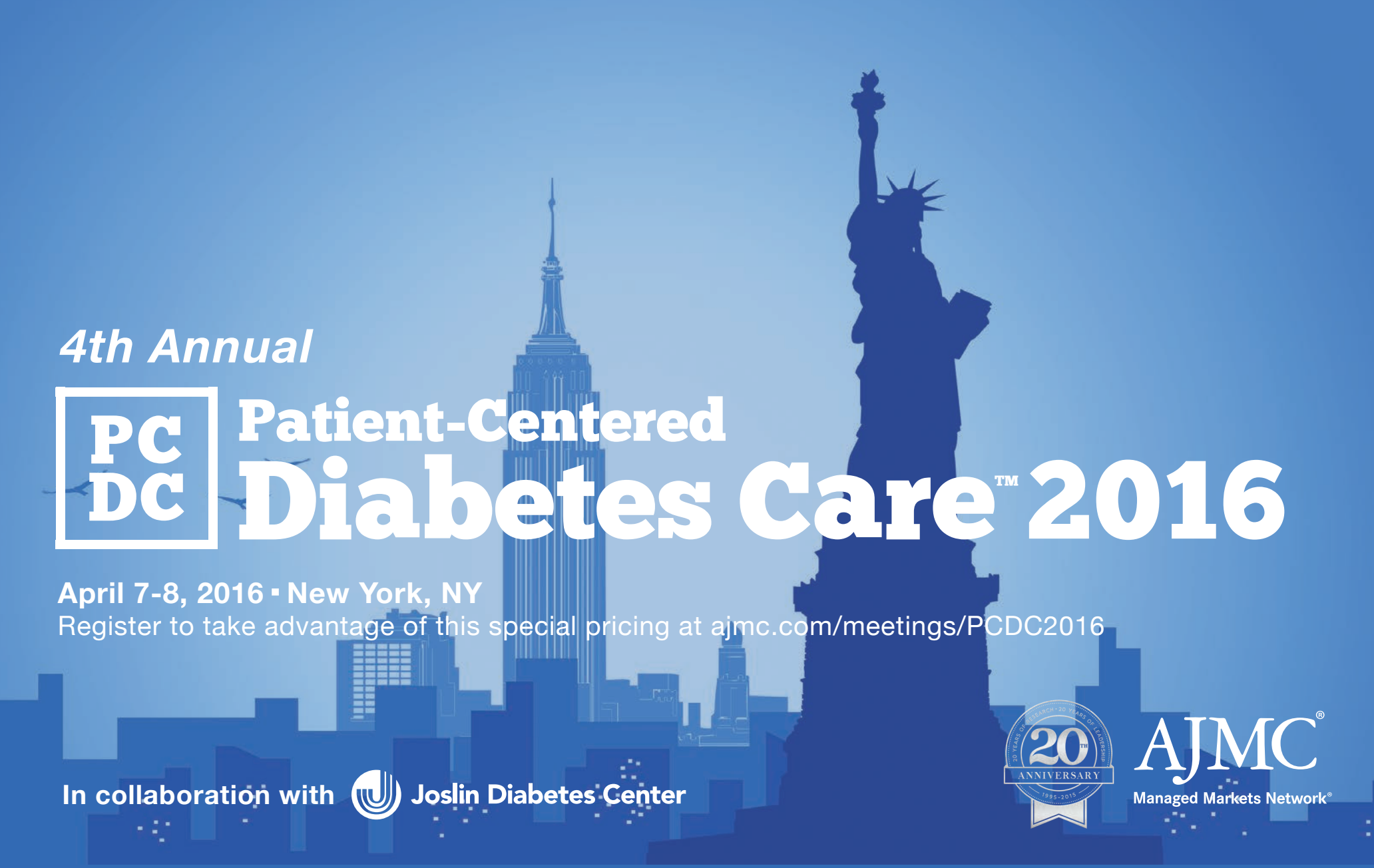
As the prices were set reaction from

(continued on page SP456)

**PHASE 3 RESULTS**

Intarcia Therapeutics Inc, announced topline results that say its ITCA 650 delivery system outperformed top-selling sitagliptlin in a clinical trial of patients with type 2 diabetes mellitus, (**SP445**).

*Also in this issue...*



*4th Annual*

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**Robert A. Gabbay, MD, PhD, FACP**
Chief Medical Officer and Senior Vice President
Joslin Diabetes Center
Associate Professor of Medicine
Harvard Medical School
Boston, MA

## LOCATION:

**New York City**

## REGISTRATION FEE INCLUDES:

- Admission to the evening networking reception on April 7th
- Admission to all sessions, presentations, and discussions on April 7th and 8th
- Breakfast, lunch, and snacks on April 8th

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|---|---|
| Before Jan 1, 2016 | $50 |
| Jan 1 - Feb 29, 2016 | $99 |
| Mar 1 - Mar 31, 2016 | $149 |
| After Mar 31 | $199 |

A cancellation fee of 25% will be assessed on refunds requested prior to **February 5, 2016**, and a 50% fee on refunds requested from **February 6, 2016**, through **March 15, 2016**. No refunds will be made after **March 15, 2016**. There is no charge for substitution. Substitutions can only be applied to the same conference, and only two substitutions will be honored.

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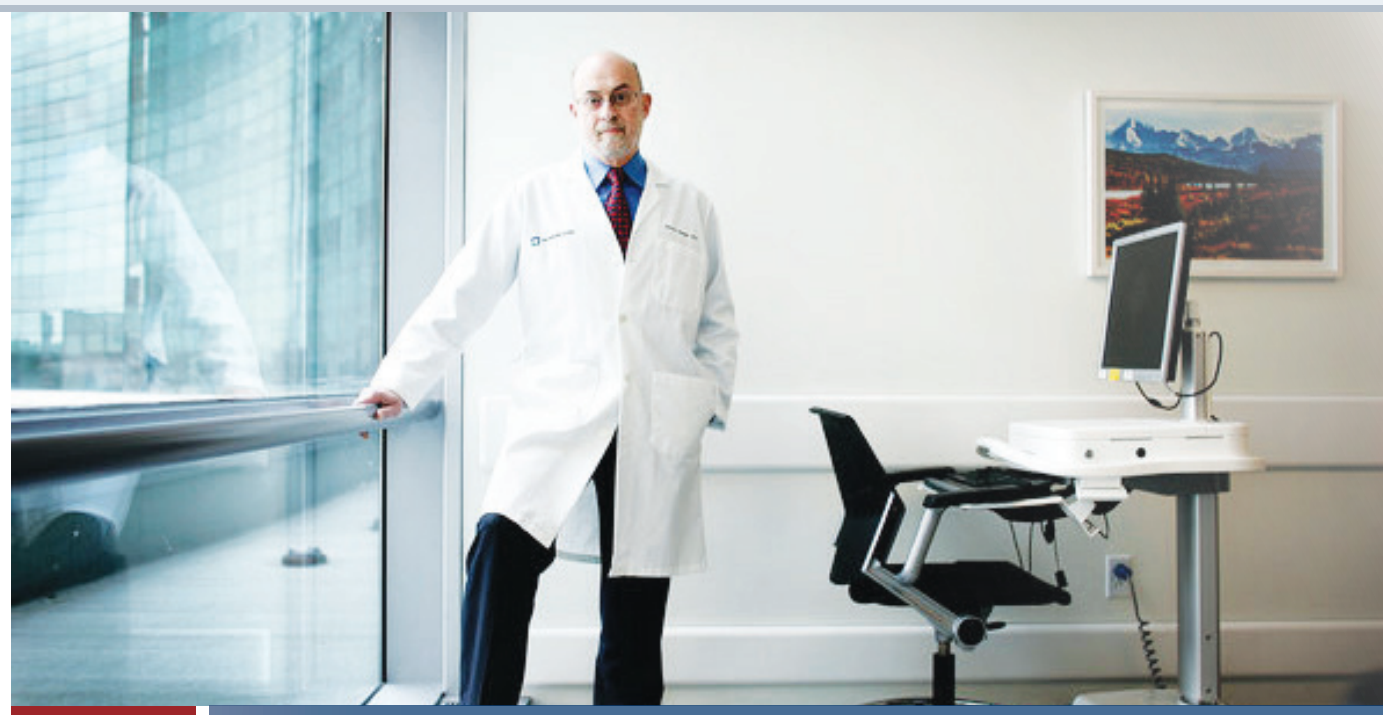

**SP447** *Steven Nissen, MD, chair of the cardiology department at the Cleveland Clinic, took the unusual step of issuing his own press release when early trial data involving the obesity drug Contrave were shared with too many officials at Orexigen. Despite the episode, the process for cardiovascular outcomes trials remains a good one, he said.*

Photo courtesy of Cleveland Clinic.

# Finding the Balance Between Behavioral Change, Therapy in Treating Obesity, Diabetes

MIKE HENNESSY, SR

This issue of *Evidence-Based Diabetes Management* examines the relationship between obesity and diabetes, and it also looks at the challenge of behavioral change. So often we hear that "lifestyle" holds the key to turning the corner, both for rising incidence of disease—especially of type 2 diabetes mellitus (T2DM), and for the rising costs of healthcare. There have been great strides in the variety and the effectiveness of the therapeutic options available to treat T2DM and obesity. One of the most recent arrivals, liraglutide, has shown impressive results in both conditions. This issue features research updates on therapies that are demonstrating added benefits beyond what we knew just a few months ago.

Payers have been willing to cover many of the new options that lower blood sugar, but drugs strictly aimed at weight loss have been a tougher sell, despite the 2013 declaration from the American Medical Association that obesity is a disease. Is this resistance tied to old sentiments that obesity is one's own fault and that people who can't lose weight just aren't trying hard enough? Perhaps, but that's shortsighted. As Osama Hamdy, MD, tells us, for many years patients were given bad nutrition advice about how to lose weight, so failing to help them now is unfair. Losing weight is difficult and complex, and as the articles in this issue show, neither medication alone nor diet and exercise alone are likely the answer. An excellent commentary by Ted Kyle, RPh, MBA, and Fatima Cody Stanford, MD, MPH, MPA, makes the case for why payers should cover obesity drugs as part of an overall effort to help patients lose weight—and why it's in everyone's interest. What we know from Dr Hamdy's research and from our own visit with patients and frontline providers at Jefferson Hospital in Philadelphia, Pennsylvania, is that behavioral change is not easy—the effort requires intense education, sustained commitment, and support. But what we know from these examples is that long-term weight loss, difficult as it is, is worth pursuing. The health effects that result from weight loss are significant, the savings are real, and the benefits can be life-changing.

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

## EDITORIAL MISSION

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





Evidence-Based Diabetes Management

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# Gathering Evidence to Understand Links Between Obesity, Diabetes

ROBERT A. GABBAY, MD, PHD, FACP

ABOUT THE EDITOR IN CHIEF

Joslin Diabetes Center

ROBERT A. GABBAY, MD, PhD, FACP

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

The connection between diabetes and obesity is hardly a secret, yet we don't fully understand this relationship as well as we should. Both type 1 and type 2 diabetes mellitus (T2DM) have been recognized as disease states for decades; sadly, obesity was only declared a disease by the American Medical Association 2 years ago.

We are learning more about this connection. In the most recent issue of *Diabetes Care,* researchers who studied a cohort of nearly 7000 patients for an average of 6 years found that being overweight increased the chances of developing T2DM over time, even if patients did not have metabolic dysfunction. Among those who did, the chances of developing T2DM soared as their weight increased.[1]

With therapies for T2DM abundant, perhaps not enough emphasis is placed on encouraging lifestyle changes. For a long time now, it's been easier to write a prescription for a pill than it has been to teach patients to embrace healthier diets, to understand how to prepare food properly, to take walks, or to lift weights. For too long, our healthcare system has been designed to pay physicians to prescribe the pill instead of the walk in the park, but that's finally changing.

Another barrier, as we learn from Joslin Diabetes Center's Osama Hamdy, MD, (see **Cover Story**) has been the tendency to view diabetes and obesity as distinct conditions; Dr Hamdy, however, sees diabetes as a component of obesity, and the true culprit in the resulting health problems. Diabetes warns us of obesity the same way a fever signals the arrival of infectious disease, he says. Treating diabetes with medication without doing anything about the body fat is a losing battle—in his view, it's time to direct more research to the cause instead of the symptoms.

Dr Hamdy has much to say about how science has failed patients over the years. Nutrition guidelines that told patients that all calories were equal and replaced protein with sugar might have allowed short-term weight loss, but too many patients gained it all back with unfortunate results. His team's work has helped rebuild the weight loss diet—emphasizing healthy protein that would support exercise and strength training, and the retention of muscle. The highly successful Why WAIT program, created by his team, engaged patients through a rigorous 12-week training period. The average participant in the program lost 9.7% of body weight, but what's more important is how many learned real lifestyle changes that have perpetuated improved health outcomes.

Following the patients for a full 5 years offered greater insight into what was possible for patients who kept the weight off. First, the long follow up proved that long-term weight maintenance after weight loss was indeed possible. Second, Dr Hamdy found that patients who lost weight showed significant improvement in their lipid profiles, even if they regained some of the weight they initially lost. Dr Hamdy's work showed that the effort required to keep off the weight rewards patients with increased insulin sensitivity; in other words, they are reversing the effects of T2DM.

These results are good for patients—and for payers, because they cut healthcare costs.

We're proud that Dr Hamdy and his team were honored at the American Diabetes Association Scientific Sessions in June 2015 with the Michaela Modan Memorial Award, which recognizes contributions to the clinical understanding of T2DM.

He also sounds the alarm about taking too much medication. There is a role for medication in treating obesity; this issue also features an excellent commentary about the role for payers in helping patients gain access to therapy to give them a good start toward shedding pounds and achieving other goals.

Balancing therapy with behavioral change—healthy diets and exercise—is a much more difficult task for doctors and patients alike. Perhaps that is why successful long-term lifestyle solutions have eluded us. That does not mean we should not try. Dr Hamdy and others featured in this issue of *Evidence-Based Diabetes Management* help us consider what is possible when patients are given the right information and tools to succeed. Elliot P. Joslin, MD, founder of Joslin Diabetes Center, long ago said there was a troika or 3 secrets to managing diabetes: insulin (or medications that came later), diet, and exercise. To date, we have spent a great deal of time and money focused on medications with a relative lack of resources devoted to the other 2 parts of the troika. As you will see in this issue, there are promising approaches that can, in fact, deliver improved outcomes for our patients. **EBDM**

REFERENCE

Franssens BT, van der Graaf Y, Kappelle JL, et al. Body weight, metabolic dysfunction, and risk of type 2 diabetes in patients at high risk for cardiovascular events or with manifest cardiovascular disease: a cohort study [published online August 25, 2015]. *Diabetes Care*. 2015; doi:10.2337/dc14-0684.

# Jardiance®

## (empagliflozin) tablets 10 mg/25 mg

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

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

* JARDIANCE is not indicated for weight loss.

### INDICATION AND LIMITATION OF USE

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

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

### IMPORTANT SAFETY INFORMATION

**CONTRAINDICATIONS**

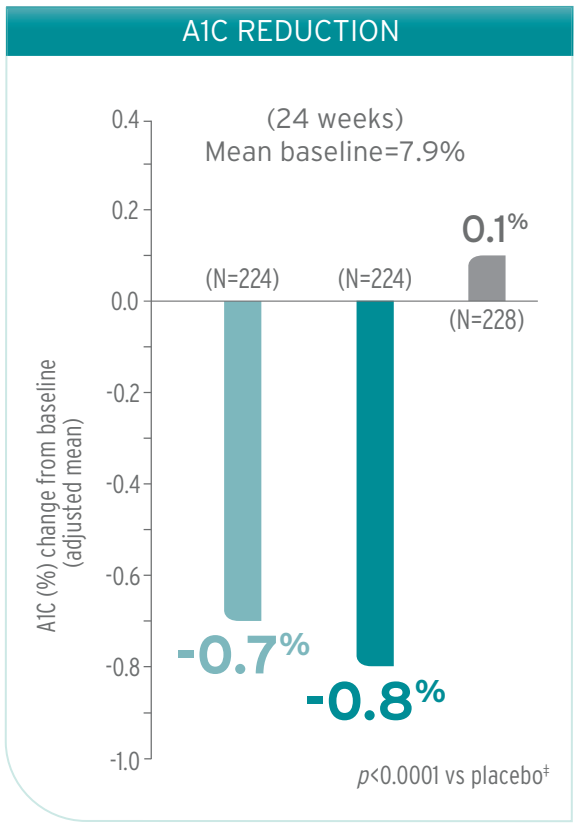
JARDIANCE should not be used in patients with a history of serious hypersensitivity to JARDIANCE or in patients with severe renal impairment, end-stage renal disease, or dialysis.

Boehringer Ingelheim

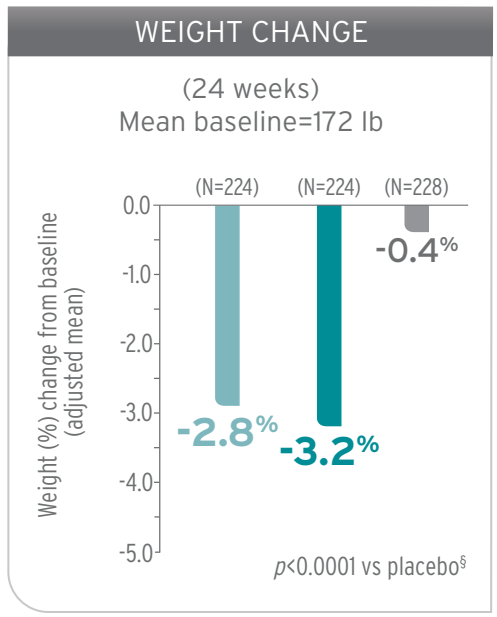
# JARDIANCE is proven to significantly reduce A1C

## In addition to lowering A1C, JARDIANCE significantly reduced weight†

JARDIANCE monotherapy vs placebo (24 weeks)




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




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

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

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

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

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

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

■ JARDIANCE 10 mg ■ JARDIANCE 25 mg ■ Placebo

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

## IMPORTANT SAFETY INFORMATION (continued)

### WARNINGS AND PRECAUTIONS

**Hypotension**

JARDIANCE causes intravascular volume contraction. Symptomatic hypotension may occur after initiating JARDIANCE particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating JARDIANCE, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy.

**Impairment in Renal Function**

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

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10 mg/25 mg

**Learn more at www.Jardiance.com**

Lilly

## IMPORTANT SAFETY INFORMATION (continued)

### WARNINGS AND PRECAUTIONS (continued)

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

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

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

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

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

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

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

### USE IN SPECIAL POPULATIONS

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

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

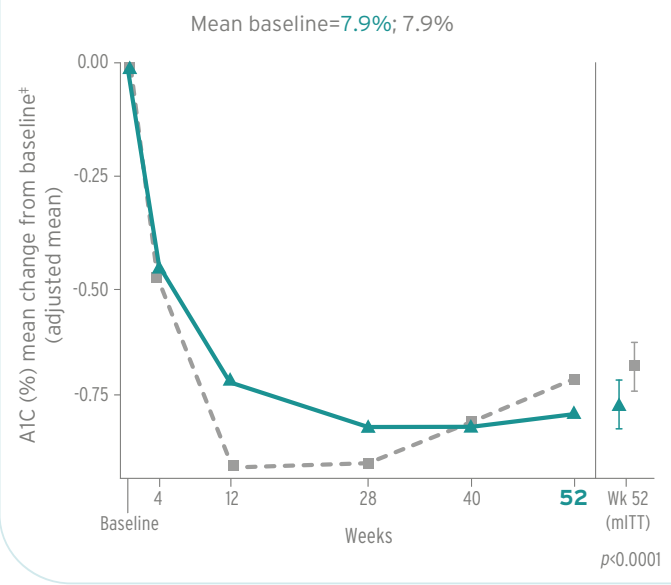
**Geriatric Use**
JARDIANCE is expected to have diminished efficacy in elderly patients with renal impairment. The incidence of volume depletion-related adverse reactions and urinary tract infections increased in patients ≥ 75 years treated
with JARDIANCE.

JARPROFISI 8.2.14

In adults with type 2 diabetes,

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

**A1C REDUCTION IN A 52-WEEK INTERIM ANALYSIS†**

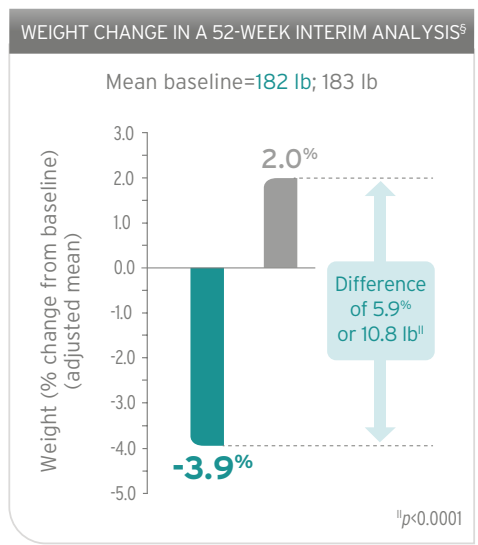



JARDIANCE 25 mg + metformin (N=693)

Glimepiride + metformin (N=700)

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

**WEIGHT CHANGE IN A 52-WEEK INTERIM ANALYSIS§**




JARDIANCE 25 mg + metformin (N=765)

Glimepiride + metformin (N=780)

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

†Completers only.

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

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

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

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

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

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

## IMPORTANT SAFETY INFORMATION (continued)

### WARNINGS AND PRECAUTIONS (continued)

**Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues**

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

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

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

Jardiance®
(empagliflozin) tablets
10 mg/25 mg

Lilly

# JARDIANCE® (empagliflozin) tablets, for oral use

$R_x$ only

## BRIEF SUMMARY OF PRESCRIBING INFORMATION

**Please see package insert for full Prescribing Information.**

**INDICATIONS AND USAGE:** JARDIANCE is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. **Limitation of Use:** JARDIANCE is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

**CONTRAINDICATIONS:**

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

**WARNINGS AND PRECAUTIONS: Hypotension:** JARDIANCE causes intravascular volume contraction. Symptomatic hypotension may occur after initiating JARDIANCE *[see Adverse Reactions]* particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating JARDIANCE, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected *[see Use in Specific Populations]*. **Impairment in Renal Function:** JARDIANCE increases serum creatinine and decreases eGFR *[see Adverse Reactions]*. The risk of impaired renal function with JARDIANCE is increased in elderly patients and patients with moderate renal impairment. More frequent monitoring of renal function is recommended in these patients *[see Use in Specific Populations]*. Renal function should be evaluated prior to initiating JARDIANCE and periodically thereafter. **Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when JARDIANCE is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin *[see Adverse Reactions]*. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with JARDIANCE. **Genital Mycotic Infections:** JARDIANCE increases the risk for genital mycotic infections *[see Adverse Reactions]*. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Monitor and treat as appropriate. **Urinary Tract Infections:** JARDIANCE increases the risk for urinary tract infections *[see Adverse Reactions]*. Monitor and treat as appropriate. **Increased Low-Density Lipoprotein Cholesterol (LDL-C):** Increases in LDL-C can occur with JARDIANCE *[see Adverse Reactions]*. Monitor and treat as appropriate. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JARDIANCE or any other antidiabetic drug.

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

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

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

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

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

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

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

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

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

| | | Pool of 24-Week Placebo-Controlled Studies | | |
|---|---|---|---|---|
| | | Placebo | JARDIANCE 10 mg | JARDIANCE 25 mg |
| Baseline Mean | N | 825 | 830 | 822 |
| | Creatinine (mg/dL) | 0.84 | 0.85 | 0.85 |
| | eGFR (mL/min/1.73 $m^2$) | 87.3 | 87.1 | 87.8 |
| Week 12 Change | N | 771 | 797 | 783 |
| | Creatinine (mg/dL) | 0.00 | 0.02 | 0.01 |
| | eGFR (mL/min/1.73 $m^2$) | -0.3 | -1.3 | -1.4 |
| Week 24 Change | N | 708 | 769 | 754 |
| | Creatinine (mg/dL) | 0.00 | 0.01 | 0.01 |
| | eGFR (mL/min/1.73 $m^2$) | -0.3 | -0.6 | -1.4 |
| | | Moderate Renal Impairment[a] | | |
| | | Placebo | | JARDIANCE 25 mg |
| Baseline | N | 187 | – | 187 |
| | Creatinine (mg/dL) | 1.49 | – | 1.46 |
| | eGFR (mL/min/1.73 $m^2$) | 44.3 | – | 45.4 |
| Week 12 Change | N | 176 | – | 179 |
| | Creatinine (mg/dL) | 0.01 | – | 0.12 |
| | eGFR (mL/min/1.73 $m^2$) | 0.1 | – | -3.8 |
| Week 24 Change | N | 170 | – | 171 |
| | Creatinine (mg/dL) | 0.01 | – | 0.10 |
| | eGFR (mL/min/1.73 $m^2$) | 0.2 | – | -3.2 |
| Week 52 Change | N | 164 | – | 162 |
| | Creatinine (mg/dL) | 0.02 | – | 0.11 |
| | eGFR (mL/min/1.73 $m^2$) | -0.3 | – | -2.8 |

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

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

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

| **Monotherapy (24 weeks)** | **Placebo (n=229)** | **JARDIANCE 10 mg (n=224)** | **JARDIANCE 25 mg (n=223)** |
|---|---|---|---|
| Overall (%) | 0.4% | 0.4% | 0.4% |
| Severe (%) | 0% | 0% | 0% |
| **In Combination with Metformin (24 weeks)** | **Placebo + Metformin (n=206)** | **JARDIANCE 10 mg + Metformin (n=217)** | **JARDIANCE 25 mg + Metformin (n=214)** |
| Overall (%) | 0.5% | 1.8% | 1.4% |
| Severe (%) | 0% | 0% | 0% |

| Table 3 (cont'd) | | | |
|---|---|---|---|
| **In Combination with Metformin + Sulfonylurea (24 weeks)** | **Placebo (n=225)** | **JARDIANCE 10 mg + Metformin + Sulfonylurea (n=224)** | **JARDIANCE 25 mg + Metformin + Sulfonylurea (n=217)** |
| Overall (%) | 8.4% | 16.1% | 11.5% |
| Severe (%) | 0% | 0% | 0% |
| **In Combination with Pioglitazone +/- Metformin (24 weeks)** | **Placebo (n=165)** | **JARDIANCE 10 mg + Pioglitazone +/- Metformin (n=165)** | **JARDIANCE 25 mg + Pioglitazone +/- Metformin (n=168)** |
| Overall (%) | 1.8% | 1.2% | 2.4% |
| Severe (%) | 0% | 0% | 0% |
| **In Combination with Insulin (18 weeks[c])** | **Placebo (n=170)** | **JARDIANCE 10 mg (n=169)** | **JARDIANCE 25 mg (n=155)** |
| Overall (%) | 20.6% | 19.5% | 28.4% |
| Severe (%) | 0% | 0% | 1.3% |

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose
[c]Insulin dose could not be adjusted during the initial 18 week treatment period

*Genital Mycotic Infections:* In the pool five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with JARDIANCE compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either JARDIANCE 10 or 25 mg. Genital mycotic infections occurred more frequently in female than male patients (see Table 1). Phimosis occurred more frequently in male patients treated with JARDIANCE 10 mg (less than 0.1%) and JARDIANCE 25 mg (0.1%) than placebo (0%). *Urinary Tract Infections:* In the pool five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with JARDIANCE compared to placebo (see Table 1). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Warnings and Precautions and Use in Specific Populations]*. *Laboratory Tests:* Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with JARDIANCE. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively *[see Warnings and Precautions]*. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups. Increase in Hematocrit: In a pool of four placebo-controlled studies, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in JARDIANCE 10 mg and 2.8% in JARDIANCE 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

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

**USE IN SPECIFIC POPULATIONS: Pregnancy:** ***Pregnancy Category C:*** There are no adequate and well-controlled studies of JARDIANCE in pregnant women. JARDIANCE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on results from animal studies, empagliflozin may affect renal development and maturation. In studies conducted in rats, empagliflozin crosses the placenta and reaches fetal tissues. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. **Nursing Mothers:** It is not known if JARDIANCE is excreted in human milk. Empagliflozin is secreted in the milk of lactating rats reaching levels up to 5 times higher than that in maternal plasma. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from JARDIANCE, a decision should be made whether to discontinue nursing or to discontinue JARDIANCE, taking into account the importance of the drug to the mother. **Pediatric Use:** The safety and effectiveness of JARDIANCE in pediatric patients under 18 years of age have not been established. **Geriatric Use:** No JARDIANCE dosage change is recommended based on age. A total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. JARDIANCE is expected to have diminished efficacy in elderly patients with renal impairment *[see Use in Specific Populations]*. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively *[see Warning and Precautions and Adverse Reactions]*. **Renal Impairment:** The efficacy and safety of JARDIANCE were evaluated in a study of patients with mild and moderate renal impairment. In this study, 195 patients exposed to JARDIANCE had an eGFR between 60 and 90 mL/min/1.73 $m^2$, 91 patients exposed to JARDIANCE had an eGFR between 45 and 60 mL/min/1.73 $m^2$ and 97 patients exposed to JARDIANCE had an eGFR between 30 and 45 mL/min/1.73 $m^2$. The glucose lowering benefit of JARDIANCE 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function. The efficacy and safety of JARDIANCE have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. JARDIANCE is not expected to be effective in these patient populations *[see Contraindications and Warnings and Precautions]*. **Hepatic Impairment:** JARDIANCE may be used in patients with hepatic impairment.

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

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



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# What "Behavioral Change" Looks Like From the Front Lines: *Visiting Jefferson Hospital*

MARY K. CAFFREY


ABOUT THE EXPERTS

CHERYL MARCO, RD, LDN, CDE

Ms Marco is director of the Comprehensive Weight Management Program, Jefferson Hospital.

LISA COCO, CRNP, CDE

Ms Coco is in the Department of Endocrinology, Diabetes and Metabolic Diseases, Jefferson Hospital.


*"It's a huge relief for the patient to learn that this is not a character flaw. 'I'm not overweight because I'm an inferior human being.'"*

—CHERYL MARCO, RD, LDN, CDE
DIRECTOR, COMPREHENSIVE WEIGHT MANAGEMENT PROGRAM

Each of the 7 women took her seat at the table, and most waited for a single grocery bag to be dropped at her feet. A bundle that contains 800 calories a day for an entire week takes up remarkably little space, but none of the women in that room at Jefferson Hospital in Philadelphia, Pennsylvania, remarked on the size of the bags or their contents.

They were not here to talk about food. That would come later.

Before they would learn how to eat all over again, the women had to learn to recognize both the physiological and behavioral triggers that had brought them here in the first place.

Their guide would be Cheryl Marco, RD, LDN, CDE, who has spent just over half of her 30-year career at Jefferson, where she is the director of its Comprehensive Weight Management Program. In that time, Marco has won awards from Optifast, coauthored peer-reviewed articles,[1,2] and appeared at symposia to highlight the program.[3]

But most of her time is spent with patients—up to 100 a week. Many have tried and failed at other diets, having never fully grasped the meaning of "behavioral change." The concept is mentioned often in papers and at conferences as the key to reversing the US crisis with diabetes and obesity.

The terms "behavioral change" and "obesity" appear together in 132 articles in PubMed, including 39 just since 2013.[4] And yet behavioral change remains elusive for many of the 78.6 million Americans that CDC estimates are obese in the United States.[5]

Jefferson Hospital allowed *Evidence-Based Diabetes Management* to visit with Marco and with Lisa Coco, CRNP, CDE, to learn what "behavioral change" means to those on the front lines at an urban hospital. While Marco works with patients who have tried almost everything to lose weight, Coco's patient population includes "the toughest of the tough." Jefferson's Department of Endocrinology, Diabetes and Metabolic Diseases works with patients with both type 1 (T1DM) and type 2 diabetes mellitus, including those enrolled in clinical trials.

While Coco said some of the newer therapies, especially sodium glucose cotransporter-2 (SGLT2) inhibitors, are effective in helping patients with diabetes achieve glycemic control, creating and sustaining behavioral change are hard work, and socioeconomic factors make a huge difference. It's essential to encourage patients to eat properly and exercise—and Coco emphasized the need to *encourage* them, because therapy alone is not enough. As the CDC's Ann Albright, PhD, RD, put it last spring in launching the Prevent Diabetes STAT initiative: "You can outeat any medication."[6]

The women had come on this particular day to talk about willpower, which Marco described as a muscle: It is strongest early in the day, and it gets weaker as people tire, as stress accumulates, and as the number of decisions mounts throughout the day. Understanding willpower, said one woman, had taught her to steer clear of a certain Chinese restaurant during trips through her neighborhood. "I don't walk that way any more," she said.

In a separate interview, Marco said that participants in the weight management program learn specific strategies: Grocery shopping should be done early in the day, when it's less tempting to buy unhealthy snacks. These hours are also a good time for preparing evening meals to be eaten later; cooking when one is hungry makes it easy to indulge while cooking. Much of behavioral change means learning to plan ahead to reduce the number of late-day decisions, Marco said; this limits the opportunity for unplanned eating in an impulse-driven culture.

Behavioral change also means making one's health a priority, instead of being overwhelmed by work and family matters. "Every single one of us is putting our job before ourselves," a woman told the group, as the rest nodded in agreement. Another shared how she sat her husband and daughter down to set the ground rules when she started Jefferson's program—if she would be following an 800-calorie diet for 12 weeks, they would have to cook their own meals for a while. "Kids have to be told," she said.

The patients who come to Marco typically have a body mass index of 30 or higher; most are women, and many are motivated after experiencing a health scare related to their weight. The program requires a commitment of time and money. The full program, which has 3 phases, costs $600 for 8 months; patients also spend $105 a week on replacement meals for the first 12 weeks, which is offset by what they are not spending on food at home. The program is not covered by insurance. All must attend an orientation session and have medical clearance to participate.

For the first phase, each participant is required to take part in weekly counseling sessions. The early sessions are not about food—topics include the genetics and physiology of obesity, as well as metabolic syndrome. Patients also learn "why we are biologically driven to eat what is in front of us," Marco said.

When patients understand the science behind their size, "It's a huge relief for the patient to learn that this is not a character flaw," Marco said. "I'm not overweight because I'm an inferior human being.'"

Why meal replacement for weight loss?

Marco said the strategies for weight loss and long-term weight management are not the same; for patients with diabetes, taking the pounds off quickly can mean getting them off some medications (Jefferson's program advertises an average 15% to 20% weight loss). This can mean reducing side effects and even putting money back in their pocket.

Once patients have completed the first 12-week phase, they transition to a second phase, called "Beyond Diets," which includes sessions on carbohydrates, superfoods, meal planning, and how to eat in restaurants. These classes enroll a mix of graduates from the 12-week meal replacement program and others who simply want to learn about healthy eating; some are patients with diabetes referred by Coco. A third phase, for maintenance, provides long-term support for keeping weight off.

## "EVERY PATIENT IS TRULY DIFFERENT"

Lisa Coco is running late. She rounds the corner at full speed, while her face stays turned in the direction of her last patient, as she gives a final set of instructions.

Twenty minutes per person is not enough for much of the population Coco serves, which includes some of Philadelphia's poorest and sickest patients who start out with glycated hemoglobin (A1C) readings of 14% or higher. Coco sees wealthier patients, too, and she'll tell you upfront that it's easier to lose weight and get diabetes under control when you live on the higher end of the economic ladder.

"I don't like treating people off an algorithm, because every single person is truly different," she said. "This patient I just saw—this is why I was late—she has an adult child in her 30s who is autistic." Coco knows that the challenge of caring for the adult child affects the patient's ability to manage her diabetes.

"There are *so* many factors," she said, still catching her breath. For patients on Medicaid, simple things like getting testing supplies covered can be a challenge. Coco holds a copy of a blood sugar chart and shows how the patient had recorded a blood sugar reading each day, giving Coco valuable information to direct her treatment.

"Labs are great, but I *need* sugars," Coco explained. When a patient has trouble getting testing supplies, "I have to write letters; I know how to work around it. But it's a huge issue."

She sees inner-city grandparents who are caring for grandchildren, patients who are overweight who she knows would benefit from talking a daily walk. "But if you walk outside, you may take a chance that someone is going to mug you or beat you up." The violence is why Coco sees young patients who are overweight, from being inside playing video games.

In her view, getting overweight diabetic patients to exercise is more difficult than getting them to change their diet, in part because of these barriers. A daily swim in a pool would do wonders for her patients who need knee replacements, but for many, "there's absolutely no access."

But when Coco can get patients with diabetes to exercise, it works. "Walking is the single best thing; it uses the excess sugar in the blood." She tries to get patients to start with a 10-minute walk and gradually increase the time; later, she encourages them to walk with half-pound weights.

Praise works, and so does understanding that progress may be measured in small steps, Coco said.

"Once in a while you get through."

## "ARE THEY IN THE TRENCHES LIKE ME?"

The promise of the new therapies to treat diabetes has been tempered by efforts to hold down costs, which may not be fully explained to providers like Coco. A trend among pharmacy benefit managers (PBMs) to seek discounts by offering exclusive deals for a single therapy in a class means constant change for those on the front lines. A patient who is doing just fine on a new SGLT2 inhibitor or injectable often has to shift to a new one—typically at the start of a new calendar year—if the health plan or PBM changes to a different preferred therapy.

But Coco remains enthusiastic about many of the new therapies, especially the SGLT2 inhibitors. Glycemic control is excellent relative to other therapies and so is adherence, she said. Plus, the class works with all insulin types, which makes prescribing easier. Coco said her experience is consistent with reports in *Evidence-Based Diabetes Management* that the class has positive effects on hypertension, so therapy for high blood pressure can be reduced or eliminated.[7]

Coco said she wishes she had grant funds to send her most motivated patients to the full schedule of food classes that Marco teaches. While she believes the price is a great value, "for people on Medicaid it's not affordable."

As much as she can, Coco takes time to teach her patients about diet, exercise, and the connections to their diabetes and weight gain. "An informed patient is someone who does better," she said, and unfortunately, sometimes physicians are not well suited to the task. "Overweight patients are *not* taught, and they are instantly judged," she said.

"With someone like Cheryl or me, it's different. I can't tell you how many times patients have written to me, 'Nobody's ever explained this to me. No one has ever told this to me.'"

She has heard about movement toward value-based reimbursement, and not everything she has heard makes her happy. CMS has announced that starting in 2016, 30% of all Medicare reimbursement will be tied to alternate payment models, with that share rising to 50% by 2018. Coco shares the concern among clinicians at urban hospitals that even if they achieve significant progress with their patients with diabetes, the American Diabetes Association targets for A1C of < 7% and < 8% for certain populations (history of hypoglycemia, limited life expectancy, or vascular complications) may be out of reach.[8] (The National Quality Forum standard used by CMS to rate accountable care organizations is < 8%.) CMS' failure to account for populations that urban teaching hospitals serve is a source of some controversy; an August article in *Health Affairs* found that 1 in 3 teaching hospitals was penalized under all 3 such measures used by Medicare.[9] A study presented in March 2015 at the annual meeting of the American College of Cardiology raised similar concerns; it found that urban teaching hospitals scored higher than suburban counterparts on quality measures for treatment of myocardial infarction but still had higher mortality rates because of the underlying health conditions of the populations they served. The study's presenter, Jacob A. Udell, MD, PhD, said the implications for CMS reimbursement policies are significant.[10]

For Coco, such policies ignore the time it takes to care for and educate the very ill patients who come to her clinic: "If I start with an A1C of 14% or 16%, even 18%, and I get them down to 9% or 10%, I've done a really good job," she said. "That might be all I'm going to be able to get them to."

"I'm only supposed to get 20 minutes for an appointment—sometimes I stay 40 minutes." Some of her patients are "65 years old; they need a knee replacement—they're not going to go run a marathon. I have them doing chair exercises. But I'm not going to get reimbursed because I didn't get them to 7%? That's very upsetting. That's so wrong," she said.

"These people making the rules—are they clinical? Are they in the trenches like I am?"

## "I KNOW MYSELF SO WELL NOW"

Cheryl Marco doesn't let people off the hook. She asks each participant in the Comprehensive Weight Management Program to state why he or she wants to lose weight, and vague answers like "health" are not allowed.

She recalls 1 severely overweight patient with T1DM, who arrived with an oxygen tank and a wheelchair. The woman's goal: She wanted to shop for clothing at a regular department store, "like Macy's." As the pounds came off, the oxygen went first, then the wheelchair.

"The day she was able to drive here was a cause for celebration," Marco said.

But the woman was not finished. She was not satisfied until she had lost enough weight to shop in a department store, freed from the "plus size" department.

"Things like being able to tie your own shoes—not having to buy shoes with Velcro—things like being able to ride the rides at the amusement park—those things help people stay motivated along the way," Marco said.

Identifying those interim benchmarks, such as getting into a pair of high-heeled shoes, helps patients stay focused on their goals. And that's important when a coworker brings in donuts or friends try to lure them into eating things they shouldn't.

Most of all, Marco's sessions help those who have struggled with their weight for years, or perhaps all their lives, to get past the self-blame that is so common. "When you're in a room with 10 to 12 overweight people, there's a lot of negative self-talk going on," she said. "There are problems that have to be solved if they are going to be successful."

The session on willpower seemed less about Marco telling the women what to do than drawing out of them what they could do for themselves. One woman had stopped driving to the meeting to save money on parking, and soon realized how changing buses and walking added up to plenty of exercise. Another told her family to stop leaving bread on the counter. A third admitted that she now looked forward to the daily weigh-in that Marco recommends to keep track of progress.

After years of feeling they had no control over their weight, the women *knew* what to do.

Said one, "I know myself so well now."

**EBDM**


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# *JAMA*: High-Dose Liraglutide Causes Significant Weight Loss in Overweight Persons With T2DM

MARY K. CAFFREY

Liraglutide, at a dose of 3 mg per day, can be combined with diet and exercise to produce significant weight loss for patients with type 2 diabetes mellitus (T2DM), according to a study reported August 18, 2015, in *JAMA*.[1]

Researchers led by Melanie J. Davies, MD, of Leicester Diabetes Centre in the United Kingdom, reported an average weight loss of 6% for patients who started the study with an average body mass index (BMI) of 37. Weight loss for more than one-fourth of the patients in the randomized controlled trial exceeded 10%.

The results also suggest that patients with T2DM taking 3 mg of liraglutide may be able to scale back their use of other anti-diabetic oral medications, while maintaining good glycemic control.[1]

Davies and her team focused on the T2DM population as part of the SCALE study; these results follow the 3731-patient study reported in the *New England Journal of Medicine* on July 8, 2015, which evaluated the overall effectiveness of liraglutide in treating obesity.[2]

"To our knowledge, this is the first study specifically designed to investigate the efficacy of liraglutide for weight management in patients with type 2 diabetes and also the first study to investigate liraglutide at the higher 3 mg-dose in a population with type 2 diabetes," the authors wrote in *JAMA*. "In the present trial, liraglutide (3 mg) as an adjunct to a reduced-calorie diet and increased physical activity was effective and generally well tolerated and was significantly better than placebo on all 3 co-primary weight-related end points."[1]


The 3 mg dose of liraglutide is sold as Saxenda.

The overall study reported in *NEJM* found that 63.2% of the patients in the liraglutide group lost at least 5% of their body weight, compared with 27% on placebo; 33.1% lost 10.6%, compared with 10% on placebo.[2] Results of the SCALE study were provided to the FDA to gain approval in the United States for the 3-mg dose of liraglutide; it is approved to treat obesity in adults with a BMI of at least 30 and for those with a BMI of 27 and at least 1 weight-related condition, such as T2DM, hypertension, or high cholesterol. FDA approved the 3-mg dose of liraglutide, to be marketed as Saxenda by Novo Nordisk, on December 23, 2014. The FDA had previously approved liraglutide at doses of 1.8 mg or 1.2 mg, marketed as Victoza, to treat T2DM.[3]

**TABLE. Key Reductions in Health Measurements Reported in *JAMA*[1]**

| Average weight loss | Percent | Pounds | BMI reduction | |
|---|---|---|---|---|
| 3 mg liraglutide | 6% | 14.1 | 3 mg liraglutide | 2.2 |
| 1.8 mg liraglutide | 4.7% | 11 | 1.8 mg liraglutide | 1.7 |
| Placebo | 2% | 4.8 | Placebo | 0.8 |
| | | | | |
| **A1C reduction** | | | **Triglycerides** | |
| 3 mg liraglutide | 1.3% | | 3 mg liraglutide | -14.68 |
| 1.8 mg liraglutide | 1.1% | | 1.8 liraglutide | -9.45 |
| Placebo | 0.3% | | Placebo | 0.41 |

A1C indicates glycated hemoglobin; BMI, body mass index

## MORE WIDESPREAD USE?

Publication of the findings may lead to more widespread use of liraglutide, both in the United States and in the United Kingdom. The day before the *JAMA* results were published, a leading British nonprofit, Diabetes UK, called for more attention to the rise of the disease, better care, and greater focus on prevention, lest the resources of Britain's National Health Service be overwhelmed by the cost of serious complications such as amputations and strokes.[4] In an e-mail to *The American Journal of Managed Care*, Davies said she anticipated the results would lead to increased use of the therapy, for treatment of both obesity and diabetes, "because at the current time it really hasn't been an option, and these new data provides an evidence base."

In the United States, patient advocates have been frustrated at the slow pace of coverage for obesity therapy more than 2 years after the American Medical Association declared obesity a disease, a move that many hoped would lead to increased treatment options.[3] As the authors noted in the *JAMA* study, even moderate weight loss of 5% to 10% can improve glycemic control and other cardiometabolic risk factors and disorders, but weight loss is especially difficult for those with T2DM (see **Cover Story**).[1]

The *JAMA* findings involved 846 patients who were randomized from a larger group of 1361 patients assessed for eligibility; 423 began the study taking 3 mg of liraglutide, while 211 were given 1.8 mg of the study drug, and 212 were given placebo. The study drug was administered daily by injection with a modified insulin pen for 56 weeks. Participants were also instructed to follow a diet that reduced their intake by 500 kcal/d and increased their exercise by at least 150 minutes per week.

More patients reported gastrointestinal disorders on the 3-mg dose than on the 1.8-mg dose or placebo, and more hypoglycemia episodes were reported on liraglutide than placebo. However, pancreatitis, which has been of concern to the FDA for all diabetes and cardiovascular therapies, was not reported.

## DIABETES MEASURES

The results reported in *JAMA* highlight the needs of persons with T2DM, who are frequently taking at least 1 if not multiple antidiabetic therapies to maintain glycemic control. Besides weight loss, which was the primary end point, the study measured levels of glycated hemoglobin (A1C) and fasting plasma glucose, both compared with placebo and compared with liraglutide at a dose of 1.8 mg. Among the 411 patients who completed the study at the 3-mg dose, 278 (69.2%) achieved an A1C target of <7%, and 227 (56.5%) achieved 6.5% or less. The average change in A1C was 1.3%. The results surpassed those of patients taking the 1.8-mg dose or placebo; 66.7% of patients taking the 1.8-mg dose achieved <7% A1C and only 27.7% of those on placebo did. The 3-mg dose produced similarly positive effects for reducing overall cholesterol and triglycerides, but less pronounced effects for reducing high blood pressure relative to the 1.8-mg dose.

"These findings suggest that in addition to clinically relevant weight loss, liraglutide [at 3 mg] may offer better glycemic control over [the 1.8-mg dose] while reducing use of oral hypoglycemic agents and maintaining a low risk of hypoglycemia," the researchers wrote. The only difference in adverse events between the 2 doses was a higher incidence of nausea for the 3-mg dose.

## WEIGHT LOSS

The primary results include how much weight patients lost over the 56-week period (the study featured a 12-week follow-up to see if patients regained weight once they stopped taking the study drug). At week 56, the average weight loss was 6% or 14 lb for those on the 3-mg dose of liraglutide, 4.7% or 11 lb for those on the 1.8-mg dose, and 2% or 4.8 lb for those on placebo.

The percentage of patients who achieved weight loss of at least 5% was 54.3% for those on the 3-mg dose, compared with 40.4% on the 1.8-mg dose and 21.4% on placebo. The percentage who lost more than 10% of their body weight was 25.2% on the 3-mg dose, compared with 15.9% on the 1.8-mg dose and 6.7% on placebo.

## QUALITY OF LIFE

This study presented data on quality-of-life measures—everything from improvement in physical function to self-esteem to changes in patients' sex life. Researchers found significant improvements for those who took the 3-mg dose but not those on the 1.8-mg dose, "primarily driven by a significant improvement in the participants' physical function."

In her e-mail, Davies said, "The relationship between quality of life, weight loss, and adherence is complex; from our study it's difficult to pick out this interrelationship, but clearly there was improved quality of life—particularly functional quality of life—related to increased weight loss."

In the article, the researchers said more work would be needed to pin down the relationship to better adherence. "It is possible that such improvement in quality of life and treatment satisfaction would lead to better adherence to treatment and lifestyle interventions and reinforce desired behavior, although further studies would be needed to confirm this," they wrote.

The study in *JAMA*, as well the findings reported in July in *NEJM*, were funded by Novo Nordisk. **EBDM**

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# Intarcia Says Phase 3 Results Show Better Control Than Januvia for Type 2 Diabetes Mellitus

MARY K. CAFFREY

Intarcia Therapeutics Inc has released topline results for ITCA 650, the implantable device that can deliver up to a year's worth of exenatide, and said patients with type 2 diabetes mellitus (T2DM) in a phase 3 clinical trial experienced results superior to those of patients treated with sitagliptin, marketed as Januvia.

In results released August 18, 2015,[1] the company said patients treated with 60 mcg/d of exenatide saw an average reduction in glycated hemoglobin (A1C) of 1.5%, compared with the average reduction of 0.8 % ( $P$ <.001) for patients taking 100 mg/d of sitagliptin. The patients who were delivered exenatide, a widely used GLP-1 receptor agonist, also experienced greater weight loss, an average of 4 kg, compared with an average loss of 1.3 kg for the sitagliptin group.

The company also reported that more patients in the ITCA 650 group achieved the American Diabetes Association (ADA)-recommended target of <7% A1C.

The phase 3 FREEDOM-2 trial involved 535 adult patients with T2DM who were treated for 52 weeks, with a 4-week post treatment follow-up period. All had an A1C of at least 7.5% but not greater than 10.5%. All patients were treated with background metformin and were randomized 1:1 for treatment with either sitagliptin or with exenatide through the unique delivery system, in which a matchstick-like device is placed under the skin to continuously administer tiny doses of the drug, ensuring perfect adherence.

Intarcia is expected to file for a regulatory approval in the first half of 2016, according to the statement from the company.

"If approved, ITCA 650 would be the first and only GLP-1 receptor agonist to offer a viable alternative to regular, lifelong injections, and with once or twice yearly dosing it has the potential to enhance patient compliance, which has been a long-standing, unresolved problem and a major contributing cause of poor glycemic control over time," said Robert R. Henry, MD, chief of the VA Endocrinology and Metabolism Section and professor of medicine in residence at the University of California San Diego, and an investigator in the phase 3 trial.

The data, he said, leave little doubt about the value of the delivery system in tackling the vexing problem of medication adherence, which has been a huge obstacle to achieving glycemic control in certain patient populations.

SOURCE/Intarcia Therapeutics Inc

ITCA 650's performance head-to-head against sitagliptin is compelling in light of sitagliptin's worldwide sales of $6 billion, said Intarcia president and CEO Kurt Graves.

Sitagliptin, a DPP-4 inhibitor, scored a major victory earlier this year when it demonstrated no cardiovascular effects in the TECOS trial, especially relative to its closest competitor; topline results were released in late April and the full study was presented in June at the Scientific Sessions of the American Diabetes Association.[2] But ITCA 650 was a star at the ADA sessions in its own right, with scores of visitors crowding the booth to watch demonstrations of how the tiny drug-fueled piston was inserted under the skin. A large crowd packed a conference session to hear promising phase 2 results.[3]

While the company reported the weight loss results, it noted in its statement that ITCA 650 is not yet being investigated for management of obesity. Full data will be reported at an upcoming major medical meeting.[1] **EBDM**


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# Another Distinct Link Between Cancer and Obesity: the AEG-1 Protein

SURABHI DANGI-GARIMELLA, PHD

Emerging research has consistently pointed to the association between cancer and obesity, and 1 protein in particular is evolving as a key regulator of metabolic diseases as well as cancer. Astrocyte elevated gene-1 (AEG-1), an established oncogene and important contributor to the various steps of carcinogenesis in diverse organs and tissues, has for the first time, been associated with obesity.

Work that primarily came out of the Virginia Commonwealth University Massey Cancer Center has identified this oncogene's role in lipid metabolism. Scientists generated a mouse that did not express AEG-1 (knockout or KO); the KO mice were viable, fertile, leaner than the wild type (control) mice, and also lived significantly longer than the control mice. To test the role of this oncogene in lipid metabolism, the animals in both groups were stressed with a high fat and cholesterol diet—while the control mice showed rapid weight gain, the scientists discovered that the KO mice remained lean. An attempt to tease out the mechanism of this phenotype indicated a reduction in fat absorption from the intestines of the KO mice, while the rate of fat synthesis was not altered.[1]

An interesting observation from the study was that despite being expressed in neurons, knocking out AEG-1 did not influence feeding behavior of the KO mice. The authors believe that calorie restrictions, caused by reduced fat accumulation in the body, might account for their longevity. Regulation of lipid metabolism, they write, might also implicate AEG-1 in obesity-associated illnesses such as non-alcoholic fatty liver disease and obesity-associated cancers.[1]

"There are many labs working extensively on AEG-1, and our collective work using human cells (with overexpression and knockdown of AEG-1) and AEG-1 knockout and transgenic mice conclusively demonstrate that AEG-1 is a bona fide target for cancer and a valid target for obesity," said Devanand Sarkar, MBBS, PhD, lead author of the study in an e-mail. Sarkar is associate professor in the department of Human and Molecular Genetics, Massey Cancer Center at Virginia Commonwealth University. Indicating that their preliminary studies were conducted in a nude mouse xenograft model, he added, "We will continue our evaluations in more stringent mouse models that develop spontaneous HCC [hepatocellular carcinoma]. Once we obtain these baseline data we plan on submitting an IND [investigational new drug] application to FDA for phase 1/2 clinical trials in HCC patients."

## OBESITY AND CANCER

Of the several lifestyle factors responsible for causing cancer, including tobacco and use of tanning devices, the American Association of Cancer Research Cancer Progress Report for 2014 also listed obesity and lack of physical activity as causative factors.[2] The report attributes nearly 25% of cancer incidence to being overweight or obese, second to tobacco. Add to it a poor diet and absence of physical activity, and together they are responsible for 33% of cancer incidence. A position statement by the American Society of Clinical Oncology released in 2014 even went as far as to state that obesity is overtaking tobacco as the leading "preventable" cause of cancer.[3]

### *Survival is worse in obese cancer patients*

The American Cancer Society released a report over a decade ago indicating that obesity was an added risk for cancer-associated death in men (prostate 34%, kidney 70%, colorectal 84%, esophagus 91%, stomach 94%, pancreas >2-fold, liver >4-fold) and in women (colorectal 46%, ovarian 51%, breast 2-fold, cervical

**TABLE.** NCI-Supported Projects Related to Obesity and Cancer Risk

| | |
|---|---|
| **NCI-funded initiatives** | |
| Transdisciplinary Research on Energetics and Cancer (TREC) | Research initiatives to investigate the combined effect of obesity, poor diet, and low levels of physicial activity on cancer risk. |
| Breast Cancer Surveillance Consortium (BCSC) | Studies to examine why obese adults have lower rates of breast cancer screening. |
| National Collaborative on Childhood Obesity Reseach (NCCOR) | NCI actively participates in NCCOR activities related to measurement, surveillance, and policy evaluation. NCCOR brings together the CDC, National Institutes of Health, Robert Wood Johnson Foundation, and the US Department of Agriculture. |
| **Research and policy resources** | |
| National Health and Nutrition Examination Survey (NHANES) | NCI is supporting the use of activity monitors to collect objective physical activity, sleep, and stength data for NHANES. |
| Genes, Environment, and Health Initiative (GEI) | Invest in new technology to measure the influence of environmental toxins, dietary intake, and physical activity on an individual's genomic, proteomic, and metabolomic responses. |
| **Population studies** | |
| Prostate, lung, colorectal, and ovarian cancer screening trial | Subjects in this trial are studied to learn about the influence of obesity and physical activity on all major cancer types. |
| NIH-AARP diet and health study | Prospective study of the association between nutrition and major cancers in more than half a million men and women. |
| Cohort Consortium | Combination of >20 prospective global cohort studies that have enrolled more than 2 million people. Objective is to evaluate obesity-related factors with less common cancers, such as thyroid and gallbladder cancer. |
| Nurses' Health Study, Iowa Women's Health Study, Health Professionals Follow-up Study, Women's Health Initiative | These studies have contributed to understanding the association between weight and cancer. |

AARP indicates American Association of Retired Persons; CDC, Centers for Disease Control and Prevention; NCI, National Cancer Institute; NIH, National Institutes of Health.
SOURCE: Obesity and cancer risk. National Cancer Institute website. http://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet#q14. Accessed August 11, 2015.

3-fold, kidney 5-fold, uterine 6-fold).[4]

Two large cohort studies conducted over more than 2 decades studied the relation between prediagnosis body mass index (BMI) and survival in pancreatic cancer patients and found that higher BMI resulted in a statistically decreased survival.[5]

Complications associated with dosing in obese patients might also contribute to reduced survival. A study published in *JAMA Oncology* in July 2015 retrospectively evaluated survival in 806 ovarian cancer patients who received treatment in Kaiser Permanente Northern California healthcare settings; 30% of the 806 were obese and 31% were overweight. These patients were treated with adjuvant first-line carboplatin and paclitaxel with curative intent. Having received lower doses of chemotherapy per pound of their body weight (38% and 45% lower dose in mg/kg for paclitaxel and carboplatin) compared with their normal weight counterparts, the lower relative dose intensity was an independent predictor of mortality in these patients, the study concluded.[6]

## NCI-FUNDED RESEARCH

While research by scientists like Sarkar helps identify targets that are common to obesity and cancer, the National Cancer Institute (NCI) has rolling initiatives to provide funding support for numerous activities including web and data resources, extramural and intramural epidemiologic studies, basic science research, and dissemination and implementation.[7] The **TABLE** lists NCI-funded projects and initiatives that address the obesity and cancer risk.

Data gathered over the years have provided sufficient evidence on the negative impact of weight on cancer outcomes. We now need integrated care models to translate these findings into patient care. **EBDM**


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# Survey Finds Young Patients With Diabetes Getting Fewer Eye Exams Than Older Patients

MARY K. CAFFREY

Guidelines from the American Diabetes Association (ADA) call for those with the disease to get an eye exam at least every year—and no less frequently than every 2 years—to watch for changes that could signal the onset of diabetic retinopathy.[1]

Yet despite the risk of diabetic retinopathy, which could progress to diabetic macular edema or blindness, data reported yesterday by the National Center for Health Statistics, a division of the CDC, found that only about half of those diagnosed with diabetes in the past 5 years had seen an eye specialist in the past 12 months.[2]

According to the data from the 2012-2013 National Health Interview Survey, the likelihood of seeing an "optometrist, ophthalmologist, or eye doctor" increased with age or the number of years since diagnosis. However, the CDC bulletin suggests that young adults with diabetes are putting off health screenings and therapeutic services that could help them avoid more costly care in the future.[2]

Approximately 51.6% of those diagnosed with diabetes in the previous 5 years had visited an eye specialist within the past 12 months, compared with 57.3% of those diagnosed between 5 and 10 years ago, and 61.2% of those diagnosed more than 10 years ago.

Data showed the following breakdown by age: For those 18 to 39 years old, 38.2% had been seen in the past 12 months; for those aged 40 to 64 years, 53.8% had been seen; and 66.5% of those 65 years and older had been seen.

When stratified by current age, there were no significant differences by years since diagnosis in the percentage who visited an eye specialist in the 18 to 39 or 65 and over age groups.

In the 40 to 64 age group, those who had seen an eye specialist were much more likely to have been diagnosed 10 years ago or more (58%) than those diagnosed within the past 5 years (49%).

According to the National Eye Institute (NEI), diabetes is the leading cause of adult blindness, but those with proliferative retinopathy can reduce their risk of blindness by 95% with timely treatment and follow-up care. The key, according to NEI and ADA, is getting checked regularly and spotting deteriorating blood vessels early.[3] **EBDM**


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# Fingernail Tests May Offer Cheap, Simple Way to Diagnose Diabetes

MARY K. CAFFREY

A simple test of fingernail clippings could replace a blood draw as a way to diagnose and monitor type 2 diabetes mellitus (T2DM), with huge implications for tracking the disease in the developing world.

Research on this method by a team of Belgian researchers was reported July 28, 2015, at the 2015 American Association for Clinical Chemistry (AACC) Annual Meeting and Clinical Lab Expo in Atlanta.

The team, led by Joris R. Delanghe, MD, PhD, of the Department of Global Chemistry, Microbiology and Immunology at Ghent University, collected nail clippings from 25 people with T2DM and 25 without the disease. The clippings were ground into a powder and tested with an inexpensive FT-IR photometer to measure how much the protein in the nails had bonded with sugar molecules, a process known as glycation.

"We found a striking difference in the measurements between the control group and the patients with diabetes," Delanghe said.

In an interview with *Evidence-Based Diabetes Management,* he said replacing the standard blood test to measure glycated hemoglobin is a huge advantage. In many cultures, he said, "Taking blood is something that cannot be tolerated."

As a practical matter, blood draws present safety, refrigeration, and storage problems for public health workers. Fingernail clippings, by contrast, are stable and can be stored for weeks at high temperatures. "All the equipment you need to analyze them can be stored in a car," he said.

The concept of using fingernail clippings instead of the standard blood test grew out of discussions with graduate students, who advised that cultural barriers to drawing blood to diagnose T2DM had to be overcome. "It's a nice example of how an exchange of ideas with people from various countries can lead to a new approach for diagnosing diabetes," Delanghe said.

He is not seeking a patent on the idea, because he hopes it can be useful to public health officials in places like India and Southeast Asia where T2DM incidence is on the rise. This way, Delanghe said, "It will be available for everyone."

## A FASTER TEST FOR GESTATIONAL DIABETES

Sridevi Devaraj, PhD, director of clinical chemistry at Texas Children's Hospital and a professor at Baylor College of Medicine, Houston, presented results at AACC on July 28, 2015, that could become a faster, earlier test for gestational diabetes.

The standard biomarker, A1C, has limited usefulness during pregnancy, but the current glucose tolerance test for pregnant women takes 3 hours and requires fasting—a process that Devaraj said is quite time consuming and unpleasant. In addition, it cannot be performed until 3 months into pregnancy.

Devaraj and her team collected blood samples from 124 pregnant women and examined 3 different blood proteins. They found that the levels of 1 protein, called 1,5-anhydroglucitol or 1,5-AG, were significantly different from women already diagnosed with gestational diabetes. In addition, researchers were able to establish a cut-off level for 1,5-AG that indicated gestational diabetes.

She noted in an interview that her results are retrospective and must now be confirmed in a larger, prospective study. But Devaraj is hopeful that she is in the initial stages of developing an improved test for earlier detection of gestational diabetes, with better outcomes for mother and baby.

"The good thing with pregnant women is that they will come in for their checkups," she said. "If the lab is there, they will do it." **EBDM**



# From Contrave Saga, Renewed Faith in Trials Built on Trust

ANDREW SMITH

**ABOUT THE EXPERTS**

STEVEN NISSEN, MD

Dr Nissen is chair of the Department of Cardiology, Cleveland Clinic.

DARREN MCGUIRE, MD, MHSC

Dr McGuire is director of the Cardiology Clinical Trials Unit, University of Texas Southwestern.

Several months have passed since the Contrave safety trial imploded—enough time to learn any lessons the experience may have to offer. There is little evidence, however, that the singular, but well-publicized failure, has triggered any appetite to reform an otherwise successful system.

Trials before and since have managed to follow the established 2-part design without a hitch: a handful of corporate officials receive preliminary information they need to submit information for New Drug Applications (NDAs), while everyone else remains ignorant of the numbers, unable to taint the eventual outcome. Indeed, such trials have been required of all new diabetes drugs for several years now, and regulators seem disposed toward making it the norm for any medications thought to have potential implications for long-term cardiovascular health.[1]

"We've probably gone through a dozen of them now, and, to my knowledge, the design has worked as intended with every medication except Contrave. The whole system is a compromise between getting potentially beneficial medicines to market quickly and protecting people from unexpected harm. Using preliminary data in the first step is relatively fast, and it eliminates the risk of approving something truly disastrous, which happened every so often under the old trial regime, when the only things we considered were reductions in A1C [glycated hemoglobin] or body weight. Unfortunately, preliminary data aren't enough. We need long-term outcome data, and the continuation of the same trial with the same participants is the quickest way to get it," said Steven Nissen, MD, chair of the cardiology department at the Cleveland Clinic, in an interview with *Evidence-Based Diabetes Management*.

Nissen should understand the intention of the trial design because he was the one who proposed it to the FDA back in 2008.[2] He also has reason to understand how the Contrave safety trial came undone and whether such circumstances are likely to recur, as he chaired the investigative committee that led the study, and he doubts that he will ever see anything like it again.

Contrave is a combination of 2 other drugs, bupropion (an antidepressant) and naltrexone (an opioid antagonist most commonly used to treat alcoholism). Studies found that although the drug had little effect on a majority of individuals in the study, a significant minority did respond. In 1 large trial, 55.6% of Contrave users and 17.5% of placebo users shed at least 5% of baseline body weight in 28 weeks.[3]

Historically, the FDA has not required separate safety trials for weight-loss medications—the safety information gathered from phase 3 trials was deemed sufficient—but the perceived tendency of bupropion to raise blood pressure,[4] particularly when used in combination with a few other compounds,[5] reportedly led regulators to demand a long-term cardiovascular outcomes trial, which was dubbed the LIGHT study.

FDA officials and clinical researchers from institutions across the country agreed on the basics of the trial structure with Orexigen, the company that developed Contrave, and Takeda, the company that had agreed to market it in the United States. Some 9000 patients were to be randomized between Contrave and placebo and followed until a set number of cardiovascular events had been recorded. After the first 25% of those events occurred, an independent data monitoring committee would look to see whether Contrave use was associated with at least twice the risk of strokes and heart attacks. If not, the committee would pass the data on to an equally small number of people at the 2 companies, who would use it to complete a portion of the NDA that would only be kept private. Those few people

who knew the preliminary results would be sworn to secrecy and cut off from any connection with the trial, while everyone else continued on in ignorance for several more years.

Such a cumbersome setup was estimated to cost around $200 million,[6] but simply analyzing user records after a drug's approval provides far less information. Some would argue that cheaper methods, such as retrospective analyses, provide hardly any information at all. Consider, for example, that millions of men have been using supplemental testosterone for decades now and there is still serious controversy about whether the practice significantly increases cardiovascular risk, significantly decreases it, or has little effect in either direction.[7]

The problem, according to Nissen and others, is that randomizing patients up front is the only way to get trial and control groups that are truly comparable. Assumptions about the ostensible similarity of people who do and do not use a medication in real-life situations often prove untrue. Users turn out to be sicker or less sick than nonusers in ways that escape detection, and retroactive analysis ends up being confounded by indication. Rofecoxib (Vioxx) was prescribed to 25 million Americans and all of those records failed to alert researchers that the drug significantly increased the risk of heart attacks. Data from a randomized trial (initially misanalyzed and later correctly interpreted by Nissen and others) uncovered a problem that probably killed thousands of patients.[8]

The difficulty with analyzing real-world data gets worse when a drug gets a reputation for possibly causing some problem. Metformin, for example, got a reputation for causing lactic acidosis, so physicians were far more likely to report metformin-related cases than cases related to other drugs, and it took specific trials to dispel the myth.[9,10] As a result, the FDA tends to require long-term randomized trials to monitor outcomes in cases where it suspects possible risk.

The data from the first quarter of the Contrave trial were more than good enough to help secure the drug FDA approval in September 2014. Those early efforts to rule out the possibility that Contrave doubled the risk of heart attack or stroke found instead that the drug was associated with a 41% decrease in the risk of cardiovascular events.[11] Had the news of these results been confined to a small number of Orexigen employees whose only responsibility was transferring the data to the NDA, the trial would probably have run its expected course. However, Orexigen CEO Mike Narachi was among the group that learned of the results,[12] and although his company had signed a lengthy nondisclosure agreement with the steering committee and the data monitoring committee, Orexigen later argued that it had a more pressing fiduciary obligation to investors—an obligation to secure a new patent that covered Contrave's possible use as a cardioprotective medication. If Contrave turned out to have this benefit, it would be the first of the new diabetes or obesity drugs to do so—a potentially blockbuster result (See story on **SP449**).

"Orexigen has been working closely with and is committed to continuing to work with the FDA and others to support its regulatory obligations," the company said in a statement. "Orexigen is also committed to simultaneously meeting its obligations to other regulatory authorities in the United States, such as the SEC [Securities and Exchange Commission], and abroad, such as the EMA [European Medicines Agency], which are relevant to, and have authority over, its business. The company is similarly committed to meeting its fiduciary duties to shareholders."[13]

By the time the FDA approved Contrave, Orexigen told regulators that it had shared the preliminary trial data with more than 100 people. The FDA made no public comment at the time but later said that it determined then that the LIGHT study would no longer be sufficient to meet the outcomes data requirement. Orexigen and Takeda would therefore need to run a second trial.

The preliminary trial became fully public when Orexigen filed a Form 8-K with the SEC that explained how it had come to receive a new Contrave patent.[14] Investors were delighted. Orexigen share prices jumped 50% on the news that its weight-loss drug might also protect patients against heart attacks and strokes.[15] Investigators and regulators, on the other hand, denounced Orexigen for undermining a key safety trial.

First, the FDA released a statement that criticized Orexigen's behavior and announced the need for a new trial: "The FDA strongly urged Orexigen to protect the interim data from public disclosure, and we are very disappointed by Orexigen's actions. Even before the FDA became aware that the interim results from the LIGHT trial would become publicly available via patent applications, the agency had determined that [because Contrave had initially shared preliminary results with so many people] the LIGHT trial would not satisfy Contrave's postmarketing requirement (PMR) related to cardiovascular safety. Therefore, the FDA required Orexigen to complete a second cardiovascular outcomes trial and that requirement remains in effect."[16]

Then, a couple days later, the director of the FDA's Office of New Drugs took the highly unusual step of saying in an interview with *Forbes* that the preliminary results almost certainly would not be borne out by any completed study: "Step back and think for a second," [John] Jenkins says. "We required this study because we're concerned that Contrave may cause adverse cardiovascular events because of its effect on blood pressure and heart rate. So, the likelihood that that drug is going to have an early benefit is highly unlikely. So people need to be very cautious about making medical decisions based on these data, and we're very concerned that investigators and patients may be unwilling to be in a trial based on these data when they are likely false readings of the actual effect of the drug."[17]

Even in retrospect, experts disagree about just when the spread of the preliminary trial data compromised any eventual findings from the completed study. The FDA statement indicates the belief that 100 Orexigen employees and affiliates were enough to sink it, even though company officials had nothing to do with trial management. Nissen believes the trial could have survived that initial lapse, but not the SEC filing that made the preliminary data available to everyone. Darren McGuire, MD, MHSc, who was a member of the LIGHT study's data monitoring committee, told *Evidence-Based Diabetes Management* that he believes the study, against all odds, was still producing valuable data when it was stopped.

"The big problem with preliminary data spreading beyond its intended recipients is that it can reach study patients and site investigators and bias the results. If the preliminary data look bad, patients may drop out of the trial for fear of getting dangerous medication. If the preliminary data look good, they may drop out for fear of getting the placebo. Either way, it biases the study and control groups toward each other and thus toward a null finding," said McGuire, who codirects a heart disease research group at UT Southwestern.

"The very odd thing with the LIGHT trial was that we expected the public release of the preliminary data to produce mass defections, and perhaps defections would have ruined the trial at some point, but even 3 months after the data became public, we had not observed a change in the drop-out rate that would further bias the results—perhaps because the news didn't spread so fast as we expected, perhaps because people accepted the FDA statement that the benefits were almost certainly illusory, or perhaps because they felt a duty to go through with a trial and help provide answers…In general, patients have proven very willing to stay with these trials and risk getting the placebo, even after medications reach the market. Patients really do seem to understand that these long-term trials are the only way to know if these medications actually do improve outcomes and that their willingness to stick with trials helps everyone. That attitude, in turn, has helped to make this type of trial design effective," added McGuire.

Despite warnings from the FDA and many independent researchers that the apparent cardiovascular benefits of Contrave were almost certainly illusory, Contrave sales took off. The preliminary study data were the only data available and they appeared sufficient to convince many physicians and patients to choose Contrave over the alternatives.[18]

In late March, as sales rose, the LIGHT study's executive committee voted unanimously to end the trial and publicize its ultimate findings. As expected, by the time half of the preset number of cardiovascular events had taken place, the apparent benefits of Contrave usage had disappeared. Use of the drug through the halfway point was not associated with significantly lower—or higher—risk of stroke, heart attack, or death. Takeda reportedly agreed to several different press releases that announced this finding in different languages, but Orexigen spent 6 weeks rejecting every release that investigators proposed. On May 12, 2015, Orexigen and Takeda announced that the trial had been stopped—in a press release that contained no extra trial data.[19] Minutes later, the Cleveland Clinic issued a release of its own, a release that contained analysis of the 50% data.[18] Nissen, moreover, told several journalists that day that Orexigen had misled both patients and investors by releasing the 25% data and that it had tried to perpetuate misperceptions by blocking the release of the 50% data.

Orexigen countered with a statement: "Contrary to allegations cited today by a journalist, Orexigen has never misled patients. At the time of the patent issuance in March, we stated plainly and clearly that the effect of Contrave on CV [cardiovascular] morbidity and mortality has not been established and that a larger number of [major adverse cardiovascular events] are required to precisely determine the effect of Contrave on CV outcomes …Takeda and Orexigen agreed that the appropriate manner to wind down the study was to collect the final information from the study and then to present and publish the study results. There was pressure from the [Executive Steering Committee] to release the 50% interim data. We maintained we would not be in a position to release data without access to the full data set, which we have not had and still do not have."

Even before additional trial data came out, it seemed unlikely that another trial would ever break down in a similar fashion; the precedent of an investigator and his employer choosing to violate a confidentiality agreement to provide important information to the public in what they considered due time made it even harder to imagine. That move nullified any advantage that Orexigen had inadvertently gained through the original leak, and the fact that it went unchallenged greatly reduced the expected gain any future company could expect from any attempt to intentionally manipulate

information. Orexigen stock fell from $6.86 per share on May 11, 2015, to $5.02 per share, 2 days later on May 13—nearly $1 lower than it was before the preliminary data became public.[20] It was also announced that Takeda had asked Orexigen to pay the entire cost of Contrave's second long-term safety trial, which will be led by Nissen.

"This trial design places a good deal of trust in all parties, trust that they will meet their obligations and produce the sort of quality research that will serve physicians and patients well. Even if things had turned out far worse in this case, I think most people would support the continued use of this basic trial design, though perhaps with a few modifications. The fact that the system proved itself capable of turning a potential disaster into a tolerable outcome—and a clean slate for a second trial probably counts as a tolerably good outcome—is just another argument in its favor," said McGuire.

Nissen agrees that trust is key to the success of the 2-stage trial and says that he sees no signs that the Contrave experience has led to any general diminution of trust among researchers, regulators, and corporations.

"Are there some steps that might further decrease the risk of data leaks, like a flat ban on unblinding executives or a refusal to consider any data that has leaked out in new drug applications? Possibly," said Nissen. "For the most part, though, secrets have stayed secret, both when preliminary data have been good and when preliminary data have been bad, because nearly everyone accepts the fundamental truth that such things have to stay secret for the system to work." **EBDM**


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# Empagliflozin Is First Diabetes Drug to Hit "Holy Grail" of Cutting Heart Attack, Stroke Risk in Clinical Trial

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The SGLT2 inhibitor empagliflozin, marketed as Jardiance, became the first of the newer diabetes drugs to reduce the risk of heart attacks and stroke deaths in a clinical trial,[1] an achievement that a leading researcher recently said would be the "holy grail" of such drugs.

Eli Lilly and Company and Boehringer Ingelheim released topline results on August 20, 2015, for the EMPA-REG OUTCOME trial, which will be presented September 17, 2015, at the European Association for the Study of Diabetes in Stockholm, Sweden.[1] The results marked the first time that one of the newer class of antidiabetes drugs has been shown to not only have no adverse cardiovascular effects while helping patients achieve glycemic control, but the drug also had a cardioprotective effect.

Empagliflozin was approved by the FDA a year ago, after competitors that include Johnson and Johnson's canagliflozin, sold as Invokana.[2,3] The results raise the possibility that other drugs in the sodium glucose cotransporter-2 (SGLT2) class could produce similar benefits.

SGLT2 inhibitors work by blocking the SGLT2 protein, which would typically reabsorb glucose. Thus, sugar is expelled through the urine, lowering blood sugar levels in the body. The drug class is known to have benefits for hypertension, and patients have seen modest weight loss

In their announcement, Lilly and Boehringer said the study included 7000 patients with type 2 diabetes mellitus (T2DM) who were considered at high risk for heart attacks or strokes. Those taking the therapy saw significantly fewer cardiac deaths, nonfatal heart attacks, and nonfatal strokes when taking empagliflozin, in combination with standard therapy, than those patients taking standard therapy alone, which included statins and drugs for blood pressure. Patients were followed for an average of 3.1 years.[1]

Since the mid-2000s, the FDA has required newer diabetes therapies to be


SOURCE/Boehringer Ingelheim

studied after approval through longer term cardiovascular outcomes trials. This is done to ensure that there are no repeats of the Avandia saga; FDA had to highly restrict sales of this drug after a study in the *New England Journal of Medicine* indicated it increased heart attack risk.[4]

Two such cardiovascular outcomes trials were presented during the 75th Scientific Sessions of the American Diabetes Association in June. At the presentation of the ELIXA trial on lixisenatide—which found no cardiovascular (CV) risk or benefit—Yale Diabetes Center's Silvio E. Inzucchi, MD, said that if a therapy were ever developed that actually improved CV outcomes, "then we would have achieved the holy grail."[4] **EBDM**


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# Food Industry Discusses DGAC Call for Sugar Limits, but Many Are Cutting Back Already

MOLLY BOURG

Recommendations concerning sugar in the proposed 2015 *Dietary Guidelines for Americans* will be difficult for many to follow, according to a panel that appeared at a July food industry conference, where the speakers stressed the need to provide the public advice that is attainable.

At the same time, however, the food industry has quietly prepared for a future of less added sugar in diets.

Presenters at the Nutrition Facts Panel asked whether the proposed guidelines created "challenges or opportunities" during the July 13, 2015, session at the Institute of Food Technologists (IFT) Annual Meeting and Expo, held in Chicago, Illinois. The panel discussed the findings by the 2015 Dietary Guidelines Advisory Committee (DGAC), which identified added sugar as a cross-cutting topic of public health importance and called for a 10% calorie limit on added sugars in daily diets.[1]

Specifically, the DGAC found the following: "Strong and consistent evidence shows that intake of added sugars from food and/or sugar-sweetened beverages are associated with excess body weight in children and adults . . . Strong evidence shows that higher consumption of added sugars, especially sugar-sweetened beverages, increases the risk of type 2 diabetes (mellitus) among adults, and this relationship is not fully explained by body weight."[2]

The report concluded that the findings are "compatible with a recommendation to keep added sugars intake below 10 percent of total energy intake."[2]

Robert Post, senior director of nutrition and regulatory affairs at Chobani, stressed that consumers need something more tangible than a percentage of their diets as a target; rather, they should be given specific dietary changes that will help them stay below the 10% limit.[3] The FDA has tried over the past year to make the amount of added sugar in packaged foods more visible to the American public; in late July, the agency called for adding a "Percent Daily Value" to its declaration of "Added Sugars" on the updated Nutrition Facts label, which it first proposed updating in 2014.[4] If adopted, the "Added Sugars" portion would be listed under the "Sugars" subcategory of the "Total Carbs" section (see **FIGURE**).

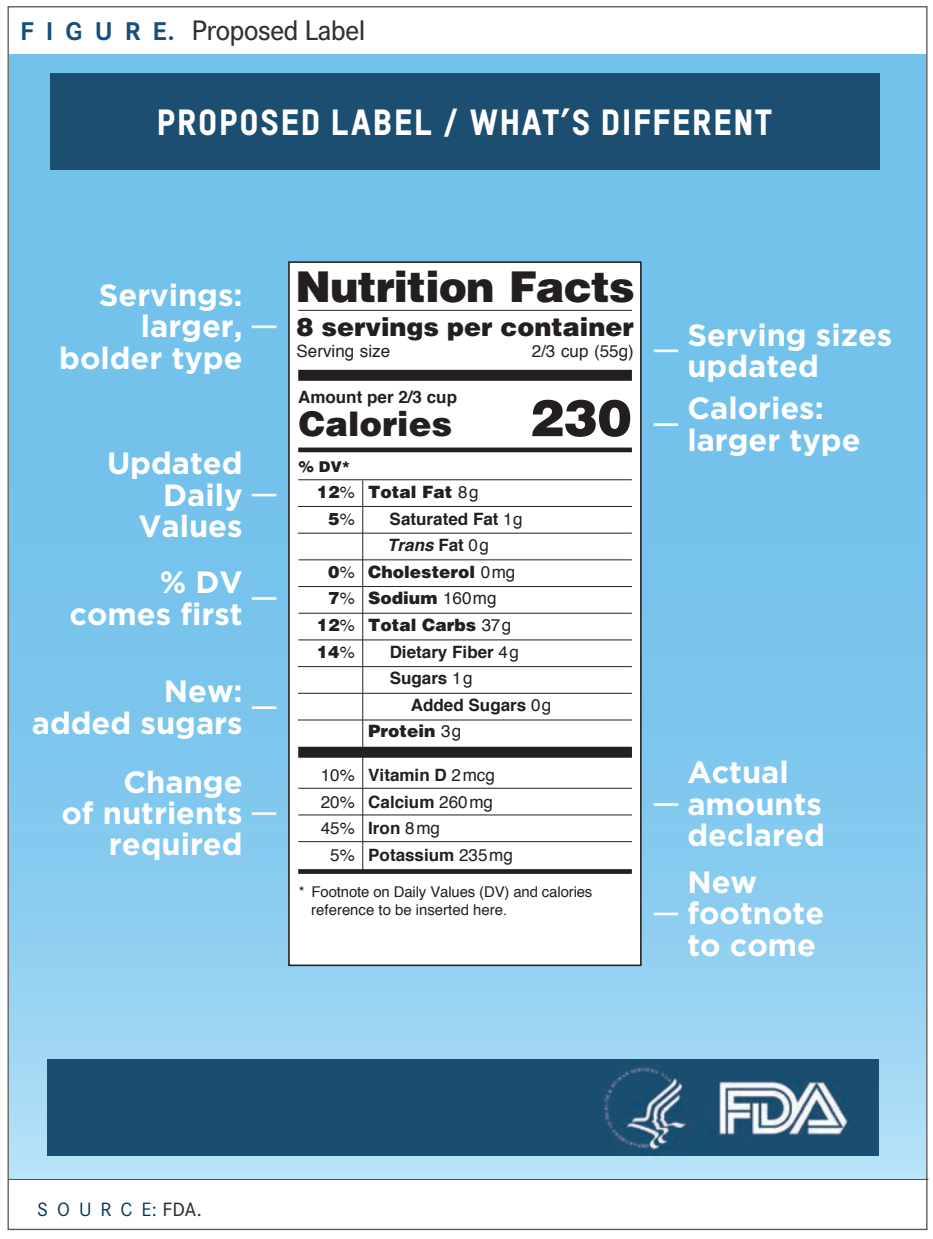
In recent years, the food industry has come under fire for using sugar as a naturally addictive ingredient in order to hook the customer, regardless of adverse health effects. Besides its pleasurable taste, sugar also serves as an important factor in optimum food texture and color. Bread, for instance, benefits from sugar caramelization that produces a pleasing brown color on the crust. Sugary coatings in breakfast cereals prevent the cereal from becoming soggy too quickly.[5] However, as IFT presenter Cassandra Soltis, corporate counsel for Starbucks Coffee Co, so succinctly states: "Added sugars have really become the new fat."

## QUIETLY CUTTING BACK ON SUGAR

To the public, refined carbohydrates and added sugars are the nutritional black sheep, which explains why many food manufacturers have not publicly complained about the 2015 recommendations. In fact, many of them have been reducing sugar in their products for years. Companies like Nestle and General Mills have been reformulating sugar content in their products since 2005.[5] Nestle has reduced the added sugar in its ready-to-drink chocolate milk products by 25% and plans to continue this process. General Mills has cut back sugar in all of its children's cereals from levels as high as 15 grams to levels of 10 grams or less.[5] These reductions have been gradual and quiet, in order to slowly acclimate the public to a different taste. This is the safe choice businesswise—an abrupt change to a classic product would incite consumer backlash. The candy maker, Mars Inc., meanwhile, has openly backed the FDA proposal to include added sugars on product labeling.[6]

While the food manufacturers have been comparatively cooperative on the DGAC's recommendation and the proposed update to food labels, the sugar

**FIGURE.** Proposed Label




SOURCE: FDA.



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industry itself is critical of such changes. The Sugar Association claimed that FDA's proposed modification to the food label, which is based on the DGAC's report, does not meet the agency's standards; the sugar group said in its statement that "It appears [the FDA] is making assertions that lack adequate scientific evidence."[7]

Americans are starting to prefer less sugar in their everyday diets. This can be seen in the popularity of low-carbohydrate dietary trends such as the Atkins diet, the South Beach Diet, and most recently, the Paleo Diet. Several recent reports suggest that after a generation of weight gain, the pendulum is moving in the other direction; the amount of full-calorie soda consumed has dropped 25% in 20 years, and in 2014, the CDC reported that the obesity rate for the youngest children had plunged 43% in a decade.[8,9] However, enacting dietary change through government action has received mixed reviews. New York City's controversial attempt to ban jumbo sodas was shot down last June by the state's highest court.[10] Some California municipalities are trying a taxation approach instead of banning products. Berkeley residents approved the nation's first soda tax last November, charging 1 cent per ounce on the distribution of sugar-sweetened beverages.[11] The measure brought in $116,000 in the first month, with the collections proposed to fund public health programs, though at present monies are going to the city general fund.[7] Berkeley's law is still new, but it appears to be a success.

In general, the public supports the movement toward less sugar in diets, and food manufacturers want to meet the demands of the customers.[12] However, there appears to be some dissonance on the methods used. Many consumers are wary of food companies replacing sugar with artificial sweeteners, and local governments are still trying to formulate the best course of action for addressing the health needs of the community. The question remains, not where are we going, but how will we get there? **EBDM**


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# If Beef Is Not Sustainable, Is Growing It the Answer?

MOLLY BOURG

ABOUT THE PRESENTER

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SOURCE/Cultured beef, Maastricht University photo.

The meat industry, and beef producers in particular, have been criticized for a lack of sustainability in a society increasingly concerned about the environment. In fact, the 2015 Dietary Guidelines Advisory Committee (DGAC) cited the need for sustainability in calling for limits on red and processed meat consumption in its February recommendations.[1]

But food scientists now have a possible solution: growing meat with stem cells.

Mark Post, MD, PhD, of Maastricht University, Netherlands, presented "Advanced Food Technology: Culturing Meat Outside of the Animal," at the 2015 Institute of Food Technologists Annual Meeting and Expo in Chicago. In this process, stem cells are extracted from an animal's skeletal muscle tissue and placed in an artificial growth environment. With proper care, these stem cells yield food-grade muscle tissue for human consumption.

While showing promise, this project remains a work in progress. Myoglobin production, for instance, has been a problem, and in past trials Post's team has had to color the final product with beet juice and saffron to achieve the familiar red hue. Since then, the researchers have lowered the oxygen levels at which the cells are grown to achieve favorable results. The meat is also 100% lean, making the texture dry and the flavor subpar.

Post says his team is already exploring measures to introduce fat into the product. However, current methods of growing fat tissue that are used by the broader research community have not met their unique needs. "The process is not compatible with food production," Post explained. "It requires a high level of steroids and cadmium, which is very toxic for people."

They've had to redesign the process, and are looking into different stimulation methods for the stem cells. Post says they have had success using branched fatty acids as stimulators.

However, the most challenging portion of the project might not be the meat itself but the public's perception of it. The public is wary of this "frankenmeat," as Post put it, which is in its own way quite logical. "We want to have at least some sense of control over how our food is being produced," said Post. He went on to explain how this production method fell into the natural versus unnatural debate within the food industry. "In an animal there's one and a half billion years of evolution; checks and balances are done by nature. If something goes wrong with it, it will cease to exist. Whereas now, it is being transferred to the hands of humans. They make mistakes; they are sometimes fraudulent."

The team has taken steps to sensitize the public to the idea of lab-grown meat. At a televised event in 2013, Post's team debuted the first in vitro hamburger, priced at $300,000, in London. Efforts to involve the community have been proposed once the meat can be produced on a larger scale. These include private growing units to be installed in consumer homes and community farms where the public would be able to meet the animals that supply the stem cells and see the food being produced. With more public acceptance and fine tuning of the project, consumers may see lab-grown meat available in a decade or so, Post said.

Maastricht University is even hosting the "First International Symposium on Cultured Meat," to be held in the Netherlands, October 18–20, 2015.[2] **EBDM**


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## Synjardy Joins Ranks of Combo Therapies for T2DM

MARY K. CAFFREY

Another combination therapy for type 2 diabetes (T2D) has entered the US market. On August 27, 2015, the FDA approved Synjardy, a combination of the sodium glucose cotransporter 2 (SGLT2) inhibitor, empagliflozin, and metformin hydrochloride. The new combination therapy was developed by Eli Lilly and Company and Boehringer Ingelheim Pharmaceuticals, who announced the FDA action in a joint statement.

Synjardy is the third therapy that includes empagliflozin. The first such therapy was approved as a monotherapy and is sold as Jardiance. The second, Glyxambi, combines the SGLT2 inhibitor with linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor.

SGLT2 inhibitors blocks the protein responsible for glucose reabsorption in the excretory system; thus, excess glucose is expelled through the urine. In this combination therapy, the SGLT2 inhibitor complements metformin, a longstanding treatment for T2D that lowers glucose production in the liver and its reabsorption in the intestines.

The FDA's action is based on findings from earlier clinical trials that involved administration of empagliflozin and metformin in combination, either with or without sulfonylurea, to treat T2D. The drug is currently available in Europe. **EBDM**

Reference

US FDA approves Synjardy (empagliflozin/metformin hydrochloride) tablets for adults with type 2 diabetes [press release]. Ridgefield, CT, and Indianapolis, IN: PRNewswire; August 27, 2015. www.prnewswire.com/news-releases/us-fda-approves-synjardy-empagliflozinmetformin-hydrochloride-tablets-for-adults-with-type-2-diabetes-300134171.html. Accessed August 31, 2015.

## Non-Surgical Balloon Device Approved to Treat Obesity

MARY K. CAFFREY

Patients being treated for obesity gained a new, nonsurgical treatment option on July 28, 2015, when the FDA approved the ReShape Integrated Dual Balloon System. This device is designed to help adult patients who are obese achieve weight loss without surgery by taking up space in the stomach.

In its statement, the FDA said the balloon "may trigger feelings of fullness, or [work] by other mechanisms that are not yet understood."

The balloon is delivered into the stomach through the mouth via an endoscopic procedure done on an outpatient basis. Patients are mildly sedated, and the process takes about 30 minutes. The balloon is used in combination with a supervised diet and exercise plan to achieve weight loss and maintain it for a short period afterward. Designed to be temporary, the FDA said the balloon should be removed after 6 months.

"For those with obesity, significant weight loss and maintenance of that weight loss often require a combination of solutions, including efforts to improve diet and exercise habits," said William Maisel, MD, MPH, acting director of the Office of Device Evaluation at the FDA's Center for Devices and Radiological Health. "The new balloon device provides doctors and patients with a new nonsurgical option that can be quickly implanted, is nonpermanent, and can be easily removed."

Approval came after a clinical trial with 326 patients who were obese with a body mass index of 30 to 40 kg/m$^2$ and who had at least 1 other obesity-related condition. In the trial, 187 patients were randomly selected to receive the balloon device; the control group underwent an endoscopic procedure, as well, but did not receive the balloon device. Those with the device lost an average 14.3 lb (6.8% of their body weight) while the control group lost 7.2 lb (3.3% of their body weight). Six months after removal, those treated with the balloon had kept off an average 9.9 lb of the weight they had lost.

Once the device is placed in the stomach, possible adverse effects include headache, muscle pain, vomiting, abdominal pain, indigestion, gastric ulcers, and nausea from sedation and the procedure. In rare cases, severe allergic reaction, heart attack, esophageal tear, infection, and breathing difficulties can occur. The devices should not be used in patients who have previously had bariatric surgery or who have inflammatory bowel disease, large hiatal hernia, symptoms of gastric emptying, are pregnant, or use aspirin daily. **EBDM**

Reference

FDA approves nonsurgical temporary balloon device to treat obesity [press release]. Silver Spring, MD: FDA; July 28, 2015. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm456296.htm. Accessed August 31, 2015.

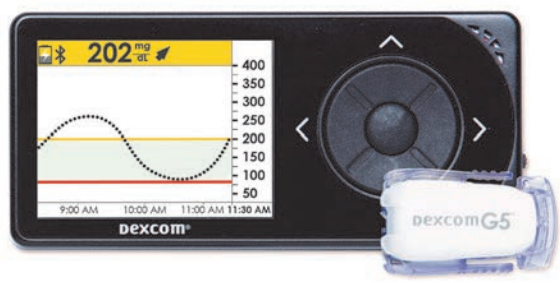
## Dexcom G5 Mobile CGM System Approved by FDA

MARY K. CAFFREY

A fully mobile continuous glucose monitoring (CGM) system, which features wireless Bluetooth technology and can be used with a smartphone, received approval from the FDA on August 24, 2015. The technology was approved for adults and children as young as 2 years who have either type 1 diabetes or type 2 diabetes.

The new technology from Dexcom, called the G5, will free users from needing a separate receiver to monitor their glucose data, giving insulin-dependent patients who use a CGM to monitor blood glucose levels long-sought advances in privacy and convenience. The Dexcom G5 mobile system is expected to start shipping in late September 2015, according to a statement from the company.

According to the company, the FDA action came faster than expected, and Dexcom will offer low-cost or no-cost upgrades to recent purchasers of its G4 Platinum and Share systems and current users who have products still under warranty.




SOURCE/Dexcom

"Dexcom is rapidly advancing technology for CGM devices to improve diabetes management. Since January, the company has introduced the G4 Platinum CGM with Share, apps to enable the first CGM on the Apple Watch, and now the Dexcom Mobile CGM," said Kevin Sayer, president and CEO of Dexcom. "These advances are making diabetes management more convenient and flexible than ever before."

Dexcom's Share technology allows users to designate up to 5 followers who can remotely monitor a patient's glucose information and receive alerts if the patient is in danger of an episode of hypoglycemia or hyperglycemia. The technology is especially usefully for parents or spouses, as a person with diabetes who experiences a drop in blood sugar may be asleep or unaware of his or her status. **EBDM**

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FDA approves Dexcom G5 mobile continuous glucose monitoring system [press release]. San Diego, CA: Dexcom, Inc newsroom; August 24, 2015. www.dexcom.com/news/1257506247-fda-approves-dexcom-g5%C2%AE-mobile-continuous-glucose-monitoring-system. Accessed August 31, 2015.

(CONTINUED FROM COVER)

its top 5 from the 2015 Scientific Sessions of the ADA.)[4]

So many previous studies have found that patients regain whatever weight they lose via short-term diet-and-exercise[5]—and often end up sicker than they started—that many physicians have come to see bariatric surgery as the only path to long-term weight loss. The new study, however, basically falsifies that belief. Indeed, considering that the median weight loss at the 5-year mark was 6.4% of baseline body weight, it suggests that savvy lifestyle management may work better than surgery. Around 53% were even able to maintain 9% weight loss from baseline.

Better still, the study also found that sustained weight loss can reduce the burden of diabetes far more than most experts had believed possible. Hamdy said earlier studies showed that with weight loss of 7% or more, insulin sensitivity improved by an average of 57%. In this recent study, patients who maintained 7% weight loss or more after 1 year were more likely to maintain their weight loss for 5 years, and maintain good diabetes control as reflected by their glycated hemoglobin (A1C) reduction.

Results were particularly good for patients who had been diagnosed with T2DM less than 5 years before the study began and had consistently managed to keep A1C levels below 7.5% with oral medication alone. Many patients with these characteristics showed partial or complete remission from diabetes. This information was presented in another poster at ADA; Hamdy and his colleagues also compared their model of Why WAIT in comparison to bariatric surgery (gastric banding). Their randomized controlled study showed no difference between the 2 interventions on diabetes control after 1 year; but the Why WAIT group showed better improvement in quality of life, especially in mental health. This study was published in the *Journal of Clinical Endocrinology and Metabolism*.[6]

The full details of the 5-year study will only become available on its publication, but such results appear to be a personal and professional triumph for Hamdy, who has devoted his career to fighting a disease that claimed the lives of many of his family members and then spent much of that career arguing to skeptical audiences that T2DM is less an independent disease than a complex symptom of obesity.

"Diabetes is to obesity as fevers are to infectious disease, yet diabetes research has typically focused on blood sugar and ignored body fat. Those priorities were always questionable, but now that many drugs can reduce blood sugar without the extra insulin that hastens disease progression, it's absurd to keep spending 80% of our research dollars developing more," said Hamdy, who runs the Obesity Clinical Program at Joslin Diabetes Center and teaches at Harvard Medical School.

Hamdy hopes that the 5-year Why WAIT data demonstrate the potential of fighting the underlying cause of T2DM rather than just managing the symptoms associated with the condition, both to research organizations that devote relatively little money to weight-loss studies and to clinicians who treat T2DM patients.

"Doctors have it drummed into their heads that long-term weight loss is impossible without surgery, so they often spend all of 30 seconds talking about nutrition and exercise before they turn their attention to medication. This study gives them a roadmap for using lifestyle modification to achieve much better outcomes over the long run."

## INTENSITY OF THE WHY WAIT INTERVENTION

Participants in the Why WAIT study underwent only 12 weeks of lifestyle intervention, but that program was very intense but doable. It included a structured diet, regular exercise, cognitive therapy, group counseling, and medication adjustment. As for the 5-year study period that followed, it mandated no particular lifestyle, though it did provide some support and required periodic check-ups, medication adjustments, and other routine care.

Many older studies had already tried something similar, and almost all of them reported depressing news. Patients lost significant amounts of weight while they followed specific diet-and-exercise programs, but once those programs ended, patients regained all the weight they lost (or more) and sometimes ended up in worse condition than they began.[7,8]

The design of the new study hypothesized that these failures stemmed largely from over-medication, muscle loss, and lackluster advice about weight maintenance.

Study diets typically restrict total calories, particularly calories from simple carbohydrates, so they raise blood sugar levels far less than standard patient diets. What's more, by reducing body fat, they steadily make patients more sensitive to their own insulin. In theory, therefore, dieting patients should need ever-decreasing amounts of medication to control blood sugar and those who have completed the diet should need less medication than they did at baseline. Yet previous studies rarely adjusted medication levels in any systematic way, said Hamdy, if they adjusted them at all. This failure created a systematic risk of overmedication, mild hypoglycemia, and intense cravings that led patients to eat themselves back to a weight that justified so much medication.

Among the key features of the new study was a custom-built algorithm that monitored how patients responded to the study regimen and adjusted their medication usage accordingly. By the end of the Why WAIT program, patients were, on average, using slightly less than half as much medication as they were before the study began. That reduction translated into an average annual cost savings of $561 per year. More importantly, it kept blood sugar levels from falling too low and encouraging patients to eat more.

Another key feature of the new study was its muscle-maintenance program. Prior studies have successfully combined diet and exercise to cause a rapid reduction in body weight, but, according to Hamdy, dieting patients typically lost almost a pound of muscle for every 3 pounds of fat they manage to shed. This muscle loss does nothing to reduce the burden of diabetes. To the contrary, research indicates that muscle loss is associated with disease progression, so Hamdy and his colleagues designed a study protocol that would minimize it. The Why WAIT study's exercise program included strength training, and its dietary guidelines called for plenty of protein. They succeeded in reducing muscle mass loss to only 10% of the total weight loss. Maintenance of the muscle mass is critical for maintaining higher basal energy expenditure (Basal Metabolic Rate, or BMR). This BMR typically goes down after weight loss and is one of the main causes of weight rebound.

Men who participated in the study ate 1800 calories a day, while women ate 1500 calories a day, which is not a drastic cut in caloric intake. Protein consumption, on the other hand, varied along with body weight: everyone received 1.5 to 2 grams of daily protein per kilogram of baseline body weight. This formula led to very protein-rich diets for heavy patients. A 250-pound woman would receive one-third of her day's calories from protein, or 150 to 200 grams a day. The diet also limited total carbohydrate consumption to no more than 40% to 45% and delivered most of them from low glycemic index carbs and fiber, rather than from sugar or starch.

The exercise program that patients performed during the initial 12 weeks of the study featured a mix of aerobic exercise and stretching, along with enough strength training to prevent muscle tloss. Given the relatively poor condition of most patients at baseline, light work with resistance bands, performed for 10 or 15 minutes a day, was generally sufficient to maintain or increase strength. The exercise program progressed gradually to 300 minutes per week by the end of the 12 weeks.

The initial regimen helped patients shed about as much weight as programs used in other trials. Patients lost an average of 23.8 pounds, which translated into 9.7% of body weight. Their body fat as content and percentage dropped significantly but ratio of lean muscle mass to fat mass went up, indicating a great preservation of lean muscle mass. Hamdy said, "this is a key indicator of successful and healthy weight loss and differentiates us from any other program."

Analysis of the study showed markedly different outcomes for the 61 patients who failed to remain at least 7% below baseline body weight for a full year (Group A) and the 68 patients who did not (Group B). Both groups dispelled the myth that long-term weight loss was impossible, but the average 5-year loss for Group A members was a modest 8.4 pounds (3.5%), while the average 5-year loss for Group B members was 23.1 pounds (9.0%), more than enough to create substantial health benefits.[9]

That weight loss had little apparent effect on simple health metrics, which may be why the abstract results did not generate much media coverage. Improvement to lipid profiles were significant and lasted the full 5 years,

ABOUT THE EXPERT


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Osama Hamdy, MD, PhD, front row, third from right, led the Why WAIT study program at Joslin Diabetes Center. He is shown here with participants and other Joslin officials, including ex-CEO John Brooks III, at Hamdy's right, followed by S. Sethu K. Reddy, MD, MBA, chief of the Adult Diabetes Section.

even among patients who regained the weight they initially lost. On the other hand, the passing of time reversed initial declines in blood pressure, even among patients who maintained significant weight loss the entire 5 years. As for A1C levels, average measurements for Group A members fell from 7.5% to 6.7% during the first 12 weeks of the study, but rose to 8% by the end of the 5 years. Group B members essentially stood still. Their average A1C level fell from 7.4% to 6.4% but climbed back to 7.3% by the end of the study, but patients were taking fewer medications.[10]

"Keep in mind that diabetes is a progressive disease, so to stop its progression or reverse it is considered a revolution in management," Hamdy said.

Such figures suggest that the effort required to keep off the extra pounds produced virtually no payoff for study patients, but other figures indicate that weight reduction rewarded patients handsomely. Not only did they enjoy the dramatic increase in insulin sensitivity—an indication that weight reduction reverses the course of T2DM—but they also enjoyed dramatically better health. According to Hamdy, the overall healthcare costs of study patients fell by an average of 27%, while the costs associated with diabetes care fell by 44%.

"No study, to our knowledge, has ever found any of this, not at the 5-year mark," Hamdy said. "We're the first to show this degree of weight loss (without surgery), this degree of disease reversal, and this degree of health and cost benefit in real-world clinical practice."

Neither the initial program nor the follow-up treatment relies on any recent discovery or technology, except perhaps the software used to keep adjusting each patient's medication. It's no secret that excessive medication leads to excessive eating,[8] that dieters tend to lose muscle, or that resistance training and protein consumption protects muscle. The diet-and-exercise regimen merely combined existing knowledge in what Hamdy considered to be a logical way when he oversaw its design. The counseling program was much the same, a collection of research-backed strategies—imperfect strategies that reflect our very imperfect understanding of self-control—for effecting long-term lifestyle changes: daily weigh-ins, meal replacements, brief spurts of exercise sprinkled throughout the day, and others.

In theory, researchers could have built a similar program and performed a similar study decades ago and, in so doing, reduced the need for gastric bypass surgery and shifted some diabetes research from A1C control to weight control. In practice, however, efforts to understand and combat diabetes have pursued what Hamdy considers a frustrating number of false leads and counterproductive strategies over the past 50 years.

"We understood the basics of type 2 diabetes a century ago: the disease is a form of carbohydrate intolerance that arises when people who are predisposed to develop it become obese," Hamdy said. "The obvious treatment, therefore, is to lose fat while reducing carbohydrates enough to control blood sugar. The creation of medical insulin moved the focus of treatment from lifestyle to medication, which seemed reasonable at the time because many people thought that diligent insulin use would be almost as good as a cure. The real problem is that after it became clear that insulin was no panacea, the focus of both treatment and research stayed fixed so completely on controlling blood sugar with insulin and, eventually, substitutes for insulin. We currently have more than 40 different drugs for diabetes management."

Those research choices affected a relatively small number of Americans while obesity remained rare, but diabetes research has become a major health issue thanks to the ongoing surge in obesity rates—a surge that Hamdy attributes in part to medical research gone wrong.

"There are a lot of reasons that we are getting fatter, but bad science did contribute," Hamdy said. "A few dubious studies led directly to bad nutritional guidelines, and from there to media coverage and advertising that spurred people to eat worse in the name of eating better. Sales records from the time show the consumption of meat and eggs and butter plummet, never to recover. Had we given obesity and nutrition the attention they deserved we would have known that replacing protein with sugar would make more people obese, but the evidence was limited and the prevailing dogma was that all calories were equal. We're still feeling the consequences, decades later, both because it takes forever to correct mistakes that get fixed in the public's imagination and because we failed to study obesity properly for so long that we don't really have all the information we need to provide clear advice about what's best."

Hamdy's obvious contempt for the food pyramid that advised Americans to subsist mainly on white flour does not indicate any support for diets that consist entirely of bacon. Up to 40% of the calories in the Why WAIT diet come from carbohydrates, albeit carbohydrates with low glycemic index values. The diet tries to keep calories from saturated fat significantly below 10% of daily intake. That said, Hamdy believes that excessive carbohydrates are the biggest problem for most T2DM patients, and he struggles to understand why many doctors still recommend that such patients get up to 60% of their calories from carbohydrates.

> *"From the beginning of the 17th century until the last part of the 20th century, diabetes was treated with a low carbohydrate diet, but over the last 4 decades we were giving our patients the wrong dietary advice that 50% to 60% carbohydrates is not a problem. It really is the problem."*
>
> —OSAMA HAMDY, MD, PHD

"From the beginning of the 17th century until the last part of the 20th century, diabetes was treated with a low carbohydrate diet, but over the last 4 decades we were giving our patients the wrong dietary advice that 50% to 60% carbohydrates is not a problem. It really is the problem."

Hamdy hopes that the 5-year figures from the Why WAIT study convince more of his colleagues about the virtues of eating carbohydrates with minimal effect on blood sugar and keeping carbohydrates well below 40% of total calories. He also hopes those results will spur many physicians to think more seriously about muscle preservation. Research has yet to prove that muscle loss causes disease progression or that muscle gain can reverse it, but many studies have demonstrated that muscle loss and disease progression are strongly associated. The Why WAIT study, moreover, provided another indication of the importance of muscle mass: the best predictor of whether a patient would sustain fat loss and enjoy disease reversal was the continuation of strength training.

"Each new piece of evidence helps us understand a little bit more about the mechanisms of both diabetes and obesity, but we still have an incredible amount to learn," Hamdy said. "It's frustrating to think that we could know so much more if we had avoided a few serious mistakes and made better research choices. On the other hand, it is a great relief to have hard evidence that we do already know enough to put together a plan that produces very significant long-term weight loss in a large percentage of diabetes patients. Now the only trick is convincing the world and, of course, learning all the stuff we need to know to make it work even better." **EBDM**


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*Disclosures*

Mr Kyle reports receiving fees for consulting services from Novo Nordisk and Eisai, Inc. Dr Stanford reports no relevant financial relationships.

it has been both hailed as a significant milestone to pave the way for more evidence-based obesity care and criticized by others as "medicalizing" a condition associated with unhealthy lifestyles.

## ACCESS TO CARE HAS BEEN LIMITED AND EXTREMELY VARIABLE

Historically, access to evidence-based care for obesity has been limited by the small number of healthcare providers skilled in obesity treatment, by inadequate treatment options, and by poor coverage in health plans. Responding to the need for more skilled providers, the American Board of Obesity Medicine has now certified 1182 diplomates in the emerging specialty of obesity medicine. The number of diplomates continues to grow, with more than 400 physicians taking the exam in 2014.[5,6]

The primary tools for evidence-based obesity care are intensive behavioral therapy (IBT), pharmacotherapy, and surgery. Coverage for IBT is improving under the Affordable Care Act (ACA) because of the requirement that effective preventive services (as determined by the US Preventive Services Task Force) be covered by health plans without any cost to patients. IBT is one of these services.

As evidence for the effectiveness of bariatric surgery has grown, coverage for bariatric surgery by health plans for people with severe obesity has also increased, though both patients and surgeons report that problems remain.[7]

Coverage for pharmacotherapy has been the most restricted of the options for obesity treatment. Drugs used for obesity treatment often have been considered "lifestyle" drugs and have been routinely excluded from prescription benefit programs, as is notably the case for Medicare Part D. In 2010, most health plans reported that 20% or fewer employers were including coverage for obesity medications in their benefits. Under the ACA, while 23 states classify bariatric surgery as an essential health benefit, only 5 states classify medical obesity treatment as an essential benefit.[8] Poor coverage for obesity medications has been identified as a key barrier to the development and introduction of improved therapies.[9]

Limited coverage of pharmacotherapy for obesity leaves both clinicians and patients with a substantial gap in options. Between low success rates with diet and exercise and much higher efficacy at a much higher cost with bariatric surgery, new and effective obesity drugs are often unaffordable.

## EVIDENCE-BASED OPTIONS ARE GROWING AND GUIDELINES ARE EVOLVING

In 2013, the American Heart Association, American College of Cardiology, and the Obesity Society jointly issued new evidence-based guidelines for the management of overweight and obesity in adults.[10] These guidelines affirmed that clinical care to reduce weight by as little as 3% and prevent further weight gain can yield significant health benefits.

Those guidelines were followed in 2014 by new evidence-based guidelines of the Endocrine Society, the European Society of Endocrinology, and the Obesity Society for the pharmacological management of obesity.[11] These drug treatment guidelines affirm the value of medications approved for chronic weight management as an adjunct to behavioral therapy for diet and exercise. They also emphasize the importance of considering the weight effects of other drugs that patients with obesity may be receiving.

Responding to the medical need for better treatment options in obesity, the FDA has approved 4 new obesity medications since 2010: phentermine/topiramate, lorcaserin, bupropion/naltrexone, and liraglutide. Each of these drugs met FDA criteria for efficacy, namely providing sustainable weight loss of 5% or more—either on average or in more than 50% of patients treated. Consistent with guidelines for obesity care, this level of efficacy was shown for each of these new drugs to provide significant improvements in diabetes, cardiovascular disease, and quality of life.

However, incorporation of these new drugs into clinical care of people with obesity has been slow, in large part due to poor coverage under drug benefit plans.[12]

## EVIDENCE-BASED OBESITY CARE CAN DELIVER GOOD VALUE

Exclusive reliance upon changes in diet and exercise to reduce the health impact of obesity is often unsuccessful. Metabolic adaptation triggers potent biological responses that act to protect an individual's highest lifetime weight indefinitely.

Economic analysis shows that 5% weight loss can deliver substantial financial benefits, even in a person with a high body mass index (BMI). Cawley et al documented the potential for savings of $2000 per year in medical costs with a 5% weight reduction in persons with a BMI above 40.[13] And because the cost curve is even steeper for people with diabetes, they found further value in preventing progression to diabetes in people with obesity.

In this analysis, the greatest economic benefit comes from the first 5% of weight loss, which is the efficacy standard for FDA approval of new obesity medicines.

Thorpe et al recently analyzed the impact of weight loss on health costs for seniors and concluded that "Medicare can realize significant cost savings through anti-obesity medications that produce substantial weight loss."[14]

## SIGNS OF CHANGE ARE EMERGING

On several fronts, tentative signs of change in coverage for obesity pharmacotherapy are visible. The AMA resolved in 2014 to press for patient access to the full spectrum of evidence-based obesity treatment, including pharmacotherapy.[15]

Also in 2014, the federal Office of Personnel Management ruled that health plans for federal employees could no longer exclude obesity medicines by characterizing them as "lifestyle" drugs.[16] The guidance further encouraged coverage of both behavioral therapy and pharmacotherapy for obesity. The National Conference of Insurance Legislators resolved in July 2015 that state legislatures should provide for "coverage of the full range of obesity treatment."[17] The growing support for access to evidence-based obesity care is beginning to show up in drug benefit plans. In 2012, Reuters reported that Express Scripts and Aetna had begun to cover new obesity drugs, phentermine/topiramate and lorcaserin.[18] More recently, CVS Caremark has been reported to have included liraglutide, the newest obesity treatment, on its 2016 formulary.[19]

Finally, legislation to open the door for obesity drugs in Medicare Part D is gaining support. The Treat and Reduce Obesity Act has been introduced in both the Senate and the House, with more than 100 bipartisan supporters.[20] It would remove the now archaic prohibition on coverage for obesity drugs by CMS.

## WITHOUT ACCESS TO EVIDENCE-BASED CARE, COSTS CONTINUE TO MOUNT

Recent suggestions that growth in the prevalence of obesity might be ending are misleading. Alhough the overall prevalence of obesity may be reaching equilibrium at an unacceptably high rate, the rate of severe obesity is continuing to grow and is driving tremendous growth in the burden of chronic diseases.[3] Obesity is a key driver, for example, of chronic liver disease, and is becoming a key factor in the growing need for liver transplantation.[21] Obesity is increasingly recognized for contributing to growth in the prevalence of many forms of cancer. All this is in addition to the long-recognized relationship with cardiovascular disease and diabetes.

So health plans are indeed paying a high price for treating the consequences of untreated obesity. Without evidence-based treatment, obesity persists, progresses, and causes chronic diseases that affect virtually every organ system.

Advising people with obesity to eat less and move more is sound advice, but it is a strategy that most people with obesity have already pursued, finding limited success. A growing body of scientific knowledge explains how the body adapts to keep people from losing their excess body weight.[22] It is now apparent that obesity will typically progress without biologically potent treatment.

As those treatments are emerging, health plan coverage will need to keep up. Without routine, evidence-based treatment, medical costs for obesity—especially severe obesity—are becoming unsustainable. **EBDM**

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## PHARMACY MANAGEMENT

*For Now, PBMs Just Say No to High-Cost PCSK9 Inhibitors*

**(CONTINUED FROM COVER)**


ABOUT THE EXPERT

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the 2 PBMs came quickly: get ready to negotiate.

CVS Health announced August 10, 2015, after alirocumab was approved and a decision on evolocumab was pending, that the PBM would not bother to talk to Sanofi-Regeneron about setting discounts until alirocumab had a competitor.[9] This move came after alirocumab's sponsors paid $67.5 million to transfer an orphan drug voucher to jump ahead of Amgen in the approval process.[10] CVS Health Chief Medical Officer Troyen Brennan, MD, MPH, told Reuters that CVS would have a management program that would take into account a patient's history of heart disease, diabetes, cardiovascular risk factors, and experience with statins before authorizing use of a PCSK9 inhibitor.[9]

**What the FDA Approved.** The PBMs are aided by the fact that labels for alirocumab and evolocumab are nearly identical. Both PCSK9 inhibitors are authorized to treat heterozygous familial hypercholesterolemia and atherosclerotic cardiovascular disease, such as heart attacks and strokes, where maximally tolerated statins are not doing enough to lower LDL cholesterol. Evolocumab received an additional indication for homozygous familial hypercholesterolemia.[2,3] While the US approvals do not cover patients who simply can't tolerate statins, which Europeans regulators allowed, they do cover enough high-risk heart disease patients that market estimates have varied from 6 to 10 million patients a year.[11]

It doesn't appear those with hypercholesterolemia will have too many problems gaining access to the drug, and CVS has indicated as much, both in an e-mail to *Evidence-Based Diabetes Management* and in public comments referencing those with "rare genetic conditions."[12] Those with high-risk heart disease will be expected to exhaust all treatment options before gaining access, however.

ExpressScripts' Chief Medical Officer Steve Miller, MD, in a statement issued the evening of the evolocumab approval, said that the drug class could become "the most costly therapy our country has seen." Until the pharmacy and therapeutics (P&T) committee completes its review in September, the drug would only be available through an exception process that will restrict PCSK9 inhibitors to those who meet the strictest terms of the FDA recommendations.[13]

Manufacturers could avoid exclusions by working with PBMs on favorable pricing. Miller said: "We would only exclude one of these products if our P&T committee determines that the product we cover is at least clinically equivalent to the one we exclude. And only then would we exclude one of these products if that exclusion would deliver significant savings for our clients and patients."[13]

CVS was less specific after the evolocumab approval, but the company inferred that most patients would have to wait until after the P&T committee had reviewed both therapies and price negotiations had occurred. "As per our standard approach, new-to-market products are not included on the formulary until they are reviewed by the CVS/Caremark Pharmacy and Therapeutics Committee and recommended for inclusion," the company said in a statement.[14]

"Based on the evaluation of the P&T committee, we will evaluate the inclusion and position of both Repatha and Praluent on our formulary. In addition, consistent with past practices, CVS/Caremark will actively negotiate with the drug manufacturers in an effort to control costs for patients and payers.[14]

Both Sanofi-Regeneron and Amgen promised that health plans and PBMs will receive discounts from the wholesale price and that programs will be created for needy patients who otherwise would lack access to the drugs. But the standoff that appeared to be shaping up in late August distressed some who observed that never before had it been so clear that payers and pharmacy managers, not doctors or even the FDA, were deciding when a drug would be appropriate. And this was happening because of price, despite the therapeutic potential.

John LaMattina, a senior partner at PureTech Ventures and a *Forbes* contributor, wrote, "The payers are making no mention of extending the lives of patients with CV [cardiovascular] disease nor the impact of reducing heart attacks and strokes to healthcare costs. This doesn't seem to be a major concern to them. Limiting their own costs, however, is paramount. Welcome to the new world of medicine."[15]

**Different Points of View.** Drug makers and PBM leaders clearly see the pricing equation differently. In announcing Praluent's price, Sanofi-Regeneron said it was inexpensive relative to other monoclonal antibodies and that pricing took into account the cost of heart disease to the US healthcare system.[4] PBMs, by contrast, fear a day when this high-priced therapy could be seen as a routine alternative to a low-cost standby, statins.[7,8,15]

The current FDA approval is not the problem, and everyone knows it. Unlike European regulators, FDA limited the scope of its approval for now while it awaits the results of long-term cardiovascular outcomes trials, which it has required since the mid-2000s to avoid letting dangerous products flood the market. While it may take until 2017

for the full results of these trials to be presented, Amgen was already touting plans to present some data at a conference days after the FDA approval of evolocumab. Of the 2 sponsors, Amgen made the stronger push at the FDA advisory committee level and at recent scientific meetings to eventually extend availability to patients who can't tolerate statins.[10,16]

Both drugs work by blocking proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme that when missing causes LDL cholesterol levels to drop by 55% to 60%, depending on the condition and whether it is used in combination with other therapy such as metformin.

The high cost of the PCSK9 inhibitor class drew the attention of the Campaign for Sustainable Rx Pricing, a Washington, DC–based group that seeks to educate lawmakers and the public about solutions to rein in the cost of new drugs. "The approval of Repatha is another example of a breakthrough medication with a too high price tag," said John Rother, president of the National Coalition on Health Care and the campaign's leader. "With several game-changing medications in the pipeline, we need to address the underlying issue of how these prices are set from the start before they hit the market."[17]

**A Return to Tight Guidelines?** CVS is not just counting on current negotiations to limit its exposure. On the same day that Brennan announced that the PBM would await a competitor in the PCSK9 inhibitor class before trying to set alirocumab's price, Chief Scientific Officer William Shrank, MD, MSHS, published a commentary in the *Journal of the American Medical Association* that calls for a return to highly specific guidelines from the American College of Cardiology (ACC) and the American Heart Association, as existed before the 2013 update that increased the pool of patients eligible to receive statins.[18]

"There is a need for consensus around management strategies for patients with high cholesterol, given that the cost differential between proven older therapies and this new class of drugs is substantial," Shrank said.[18]

ExpressScripts' Miller also called for greater specificity in the wake of the evolocumab pricing. Today's guidelines, he said, do not "provide clarity as to how these expensive new medications could fit in the treatment paradigm, potentially resulting in some scenarios where a prescriber could consider a PCSK9 inhibitor for a low-risk patient."[13]

So far there has been no word from the professional associations on such an update, but ACC President Kim Allan Williams Sr, MD, FACC, said the organization awaits the results of the long-term safety trials now under way. Full results could take as long as 2017 to complete, but it appears that Amgen at least is anxious


The FDA has approved the first 2 therapies in the PCSK9 inhibitor class. They are alirocumab, above, being marketed as Praluent by Sanofi and Regeneron; and evolocumab, being marketed as Repatha by Amgen. Pricing for both came in well above analysts' estimates.

> *"We would only exclude one of these products if our P&T committee determines that the product we cover is at least clinically equivalent to the one we exclude. And only then would we exclude one of these products if that exclusion would deliver significant savings for our clients and patients."*
>
> —STEVE MILLER, MD, CHIEF MEDICAL OFFICER, EXPRESS SCRIPTS

to present positive safety data on CV outcomes as soon as data become available.[19]

The question is whether pressure will build to make the PCSK9 class more broadly available to those who experience statin intolerance or who have high LDL cholesterol and risk factors for developing type 2 diabetes mellitus (T2DM), and whose physicians might prefer to try something other than a statin, in light of a trial that showed at least 1 statin may have hastened the progression to T2DM for those already at risk of developing the disease.[20] Since the European approval for evolocumab is already much broader and the label for alirocumab overseas will be as well,[1,21] both clinical trial and real-world data will be available over the next 2 years.

A clue to the drug makers' future arguments may have been unveiled in March, when Marc Sabatine, MD, MPH, of Brigham and Women's Hospital, discussed evolocumab's potential at the 2015 meeting of ACC in San Diego. While he insisted that statins are the "foundation" for all treatment (and deflected all questions on price), Sabatine would later make Amgen's case for extending the drug's label to statin-intolerant patients during the FDA advisory committee hearing in June. Regulators declined to do that for now, but they could change their minds should trials show long-term benefits of reducing heart attacks and strokes.[10,16]

Medicine, Sabatine said at the March meeting, has not fully considered the potential benefits of dramatically lowering LDL cholesterol in patients for whom modest reductions are currently possible. "When we think about how much we should lower LDL cholesterol, we haven't found a floor beyond which we haven't found a benefit," he said.[10] **EBDM**

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