Bridging the gap between payer and provider perspectives

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MANAGED CARE®

Evidence-Based Diabetes Management™

Payer Perspective

Optimal Health Requires More Than Medication

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Chronic conditions, such as type 2 diabetes mellitus (T2DM) and heart disease, continue to increase in prevalence and cost. The American Diabetes Association estimates that 29.1 million Americans had diabetes in 2012.[1] The healthcare cost of the 21.1 billion who were actually diagnosed totalled $245 billion, which is more than 2 times higher than nondiabetics.[2] The World Health Organization estimates that by 2030, 330 million people worldwide[3] will have diabetes. These sobering statistics only begin to tell the human story. Diabetes is the major cause of both end-stage renal disease leading to dialysis or kidney transplant and noncongenital blindness. End-stage organ failure significantly reduces the quality of life of people with diabetes and takes a major emotional toll on patients and their families.


Ed Pezalla, MD, MPH

T2DM and many other chronic conditions can be prevented, controlled, even reversed with a combination of medical treatment and lifestyle changes. Unfortunately, many people are unable to start or maintain these needed steps. A better healthcare system that treats the whole person—not only the condition—can help.

THE CRITICAL ROLE OF MEDICATIONS IN TREATMENT

No doubt, medications play a critical role in the management of chronic disease and in preventing or delaying additional more serious conditions. For example, controlling blood glucose,

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Policy Perspective

Patient Adherence and CMS Reimbursement Policies for Combination Oral Anti-Diabetic Therapies

DAVID YAO

The treatment landscape for type 2 diabetes mellitus (T2DM) has broadened greatly over the past decade with innovative therapies now targeting several distinct pathways involved in the metabolic regulation of blood glucose levels. The advent of these treatments has sparked a new race in the pharmaceutical industry to demonstrate clinical and cost-effectiveness benefits compared with standard-of-care therapies.

One noticeable trend in the development of new oral anti-diabetic products is the increase in fixed-dose combination therapy (FDCT) products, which aim to increase efficacy in lowering glycated hemoglobin (A1C) and blood glucose while reducing the side effects of the individual agents used. Several FDCT products combining metformin with a sulfonylurea, thiazolidinedione, or dipeptidyl peptidase-4 (DPP-4) inhibitor are already on the market. Other products that combine these medications with newer agents, such as the sodium-glucose co-transporter 2 (SGLT-2) inhibitors, are either in late-stage clinical trials or under FDA review. While the goal of preserving or increasing market share for a product is common among developers of these combination therapies, the benefits of these products to patients will no doubt come under increasing scrutiny from payers.

PATIENT ADHERENCE WITH FDCT

One rationale for developing FDCT products is the benefit of increasing

(continued on page SP59)

Pharma Feature

On the Horizon in Diabetes Therapy: A Delivery System That Doesn't Rely on the Patient

ANDREW SMITH

Each year, diabetes complications send more than 10 million Americans to the emergency department,[1] cause nearly 50,000 cases of kidney failure, necessitate nearly 75,000 amputations, contribute to millions of heart attacks and strokes,[2] and cost nearly $100 billion.[3,4]

The good news is that existing treatments control the disease well enough to prevent most of those problems and eliminate most of those costs. The bad news is that the majority of patients fail to follow treatment plans with the precise diligence that would keep them healthier and the healthcare system solvent.

In theory, a system that automatically gives patients just the right amount of medication at just the right time could revolutionize diabetes treatment, and that's why some researchers are so excited about an experimental product for type 2 diabetes mellitus (T2DM), ITCA 650. ITCA 650 can pack a full year's worth of a medication called exenatide into a matchstick-sized tube, which sits under the skin and dispenses a continuous trickle of treatment. Implantation takes only a few minutes and hurts little more than a single shot. Operation is automatic. Trial results are impressive.

"I have been doing diabetes research for 47 years now, and this ranks among the most exciting things I've ever seen," said Jay S. Skyler, MD, MACP, deputy director of the Diabetes Research Institute at the University of Miami's Miller School of Medicine. "It has shown itself to be truly powerful in trials to date, reducing A1C (glycated hemoglobin) levels to a remarkable degree without any effort from patients."

(continued on page SP60)

STILL SEEKING COVERAGE

Advocacy groups for persons with diabetes will keep up the pressure on both Congress and CMS to gain coverage from Medicare for continuous glucose monitoring technology. Groups cite research from *The American Journal of Managed Care* in making their case. **(SP46)**

Also in this issue...

PC DC

Patient-Centered Diabetes Care 2015

April 16-17, 2015

Renaissance Boston Waterfront Hotel
Boston, MA

Agenda

Thursday, April 16, 2015

5:00 PM to 5:40 PM
The Patient's Toolbox for Better Decision Making

5:40 PM to 6:20 PM
The Digital Path to Improved Patient Engagement in Self-Care

6:20 PM to 7:00 PM
Panel Discussion: Community as Part of the Prescription: Social Media in Diabetes Care

7:00 PM to 9:00 PM
Networking Reception

Friday, April 17, 2015

8:00 AM to 8:45 AM
Keynote Address: Robert Gabbay, MD, PhD, FACP

8:45 AM to 9:25 AM
Does National Nutrition Policy Matter? 2015 Diet and Nutrition Guideline Review

9:25 AM to 10:05 AM
Panel Discussion: Role of Clinicians and Diabetes Educators in Lifestyle Management

10:25 AM to 11:05 AM
Panel Discussion: Integrated Delivery Networks and Adherence Intervention

11:05 AM TO 11:45 AM
Matching Patients to the Right Treatment Through Personalized Medicine

12:45 PM to 1:25 PM
Finding the Balance in Lipid Management

1:25 PM to 2:05 PM
Panel Discussion: Weighing the Value of Novel Treatments in Diabetes

2:05 PM to 2:45 PM
Panel Debate: Is Two Better Than One? The Use of Combination Therapies in Diabetes Care

2:45 PM to 3:00 PM
Closing Remarks

THE AMERICAN JOURNAL OF MANAGED CARE

The American Journal of Managed Care, in collaboration with the Joslin Diabetes Center, will host its third annual Patient-Centered Diabetes Care Meeting on April 16-17, 2015, in Boston. The event will offer unique perspectives on emerging topics in diabetes care from today's leading health experts.

To register:
www.ajmc.com/meetings/pcdc2015

As a valued reader of AJMC, please use **AJMC99** in the promotional code box to register at a discounted rate of $99.

In collaboration with Joslin Diabetes Center

20 YEARS OF RESEARCH · 20 YEARS OF LEADERSHIP
20th ANNIVERSARY
1995-2015

AJMC®
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INVOKANA™ is the #1 branded therapy prescribed by endocrinologists when adding or switching non-insulin type 2 diabetes medications*

ENVISION NEW **POSSIBILITIES**

Invokana™
canagliflozin tablets

*Data on file. Based on NBRx data sourced from IMS NPA Market Dynamics Database, weekly data through 9/20/13.

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA™.
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

INVOKANA™ 300 mg demonstrated greater reductions in A1C vs Januvia® 100 mg at 52 weeks...

Adjusted Mean Change in A1C From Baseline (%): INVOKANA™ 300 mg vs Januvia® 100 mg, Each in Combination With Metformin + a Sulfonylurea[1]

- **Januvia® 100 mg + metformin and a sulfonylurea** (n=378; mean baseline A1C: 8.13%)
- **INVOKANA™ 300 mg + metformin and a sulfonylurea** (n=377; mean baseline A1C: 8.12%)

Incidence of Hypoglycemia

With metformin + a sulfonylurea over 52 weeks: INVOKANA™ (canagliflozin) 300 mg: **43.2%**; Januvia® 100 mg: **40.7%**[1]

- Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue[1]

Convenient Once-Daily Oral Dosing[1]

- Recommended starting dose: INVOKANA™ 100 mg
- Dose can be increased to 300 mg in patients tolerating 100 mg who have an eGFR ≥60 mL/min/1.73 m^2 and require additional glycemic control

*INVOKANA™ + metformin is considered noninferior to Januvia® + metformin because the upper limit of the 95% confidence interval is less than the prespecified noninferiority margin of 0.3%.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS and PRECAUTIONS

- **Hypotension:** INVOKANA™ causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m^2), elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (eg, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™ in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.
- **Impairment in Renal Function:** INVOKANA™ increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.
- **Hyperkalemia:** INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

*COVERED FOR >**75%** OF COMMERCIALLY INSURED PATIENTS WITHOUT PRIOR AUTHORIZATION*[3]

...as well as greater reductions in body weight† and systolic blood pressure (SBP)†

Change in Body Weight†

Significant reductions in body weight at 52 weeks, each in combination with metformin + a sulfonylurea (*P*<0.001)[1]

» Difference from Januvia®‡:
300 mg: **–2.8%**

Change in SBP†

Significant lowering of SBP at 52 weeks, each in combination with metformin + a sulfonylurea (*P*<0.001)[2]

» Difference from Januvia®‡:
300 mg: **–5.9 mm Hg**

INVOKANA™ is not indicated for weight loss or as antihypertensive treatment.

†Prespecified secondary endpoint.

‡Adjusted mean.

INVOKANA™ provides SGLT2 inhibition, reducing renal glucose reabsorption and increasing urinary glucose excretion.[1]

Adverse Reactions

In 4 pooled placebo-controlled trials, the most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.[1§]

References: 1. INVOKANA™ [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2013. **2.** Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care*. 2013;36(9):2508-2515. **3.** Data on file. Janssen Pharmaceuticals, Inc., Titusville, NJ. Data as of 9/17/13.

SGLT2 = sodium glucose co-transporter-2.

§Included 1 monotherapy and 3 add-on combination trials with metformin, metformin + a sulfonylurea, or metformin + pioglitazone.

Learn more at **INVOKANAhcp.com/journal**

- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.
- **Genital Mycotic Infections:** INVOKANA™ increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.
- **Increases in Low-Density Lipoprotein (LDL-C):** Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

ENVISION NEW
POSSIBILITIES

Invokana™
canagliflozin tablets

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.
- **Digoxin:** There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA™ 300 mg. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

- **Pregnancy Category C:** There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at ≥0.5 times clinical exposure from a 300-mg dose.

  These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Nursing Mothers:** It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. 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 INVOKANA™, a decision should be made whether to discontinue nursing or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.
- **Pediatric Use:** Safety and effectiveness of INVOKANA™ in pediatric patients under 18 years of age have not been established.
- **Geriatric Use:** Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA™ in nine clinical studies of INVOKANA™. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were ≥75 years of age. Smaller reductions in HbA1C with INVOKANA™ relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA™ 100 mg and -0.74% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA™ 100 mg and -0.87% with INVOKANA™ 300 mg relative to placebo).
- **Renal Impairment:** The efficacy and safety of INVOKANA™ were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥60 mL/min/1.73 m^2); patients treated with INVOKANA™ 300 mg were more likely to experience increases in potassium.

  The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), with end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.
- **Hepatic Impairment:** No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA™ has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

Janssen Pharmaceuticals, Inc.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.

November 2013 004994-131021

OVERDOSAGE

» There were no reports of overdose during the clinical development program of INVOKANA™ (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

ADVERSE REACTIONS

» The most common (≥5%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥2% of patients were male genital mycotic infections, vulvovaginal pruritus, thirst, nausea, and constipation.

K02CAN13149

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

Invokana™
canagliflozin tablets

janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

INVOKANA™

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14) in full Prescribing Information]*.

Limitation of Use: INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA *[see Warnings and Precautions]*.
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis *[see Warnings and Precautions and Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Hypotension: INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Impairment in Renal Function: INVOKANA increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA *[see Adverse Reactions]*. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

Hyperkalemia: INVOKANA can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia *[see Adverse Reactions]*.

Monitor serum potassium levels periodically after initiating INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions (e.g., generalized urticaria), some serious, were reported with INVOKANA treatment; these reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat per standard of care and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C occur with INVOKANA *[see Adverse Reactions]*. Monitor LDL-C and treat per standard of care after initiating INVOKANA.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA 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]*
- Hyperkalemia *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions]*

Clinical Studies 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 the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials: The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14) in full Prescribing Information]*. These data reflect exposure of 1667 patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions From Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Female genital mycotic infections†	3.2%	10.4%	11.4%
Urinary tract infections‡	4.0%	5.9%	4.3%
Increased urination§	0.8%	5.3%	4.6%
Male genital mycotic infections¶	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst#	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=312), INVOKANA 100 mg (N=425), and INVOKANA 300 mg (N=430).

‡ Urinary tract infections includes the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=334), INVOKANA 100 mg (N=408), and INVOKANA 300 mg (N=404).

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Pool of Placebo- and Active-Controlled Trials: The occurrence of adverse reactions was also evaluated in a larger pool of patients participating in placebo- and active-controlled trials.

The data combined eight clinical trials *[see Clinical Studies (14) in full Prescribing Information]* and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks with 1832 individuals exposed to INVOKANA for greater than 50 weeks. Patients received INVOKANA 100 mg

(N=3092), INVOKANA 300 mg (N=3085) or comparator (N=3262) once daily. The mean age of the population was 60 years and 5% were older than 75 years of age. Fifty-eight percent (58%) of the population was male and 73% were Caucasian, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 11 years, had a mean HbA1C of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 81 mL/min/1.73 m^2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.7% with comparator, 2.2% with INVOKANA 100 mg, and 2.0% with INVOKANA 300 mg) and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with INVOKANA 100 mg and 1.1% with INVOKANA 300 mg).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.9, 2.7, and 0.9 per 1000 patient-years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Upper extremity fractures occurred more commonly on INVOKANA than comparator.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2) and age 75 years and older (Table 2) *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Use in Specific Populations]*.

Table 2: Proportion of Patients With at Least one Volume Depletion-Related Adverse Reactions (Pooled Results from 8 Clinical Trials)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

***** Includes placebo and active-comparator groups

† Patients could have more than 1of the listed risk factors

Impairment in Renal Function: INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 3). Patients with moderate renal impairment at baseline had larger mean changes.

Table 3: Changes in Serum Creatinine and eGFR Associated with INVOKANA in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

			Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**INVOKANA 100 mg N=90**	**INVOKANA 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

***** Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9% with placebo, 18% with INVOKANA 100 mg, and 22.5% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 3.4% with INVOKANA 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=1085) with baseline eGFR of 30 to less than 60 mL/min/1.73 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), the overall incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

Use of INVOKANA was associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 8.9% with INVOKANA 100 mg, and 9.3% with INVOKANA 300 mg. Discontinuations due to renal-related adverse events occurred in 1.0% with placebo, 1.2% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg *[see Warnings and Precautions]*.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 3.2%, 10.4%, and 11.4% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents *[see Warnings and Precautions]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.6%, 4.2%, and 3.7% of males treated with placebo, INVOKANA 100 mg, and

INVOKANA™ (canagliflozin) tablets

INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

Hypoglycemia: In all clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14) in full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 4) *[see Warnings and Precautions]*.

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0
In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Laboratory Tests: *Increases in Serum Potassium:* Dose-related, transient mean increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 3 weeks) in a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*. In this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. More severe elevations (i.e., equal or greater than 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. In patients with moderate renal impairment, increases in potassium were more commonly seen in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions]*.

Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was 8.1% and 9.3% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Serum Phosphate: Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo controlled trials, the mean change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Warnings and Precautions]*.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

DRUG INTERACTIONS

UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Digoxin: There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were

A New Look for *EBDM*, and an Opportunity to Engage Stakeholders on Important Developments in Diabetes

We are sure you've noticed that *Evidence-Based Diabetes Management* has a new look to start 2015. We will be doing more to invite contributors from the payer, provider, pharmaceutical, and research communities to offer their perspectives on important topics in diabetes care, as well as giving you updates from the field. Our current issue takes on the difficult topic of medication adherence, which creates frustration across the healthcare spectrum. The well-known statement from former Surgeon General C. Everett Koop—drugs don't work in people who don't take them—is just the tip of the problem. Some patients won't admit they aren't taking their pills, leading to increased doses that aren't needed. Some can't afford all of their drugs, so they pick and choose which ones to take. Still others are overwhelmed by the number of pills and dosing schedules, and simply give up. This issue addresses all of these challenges, and also presents an exciting new technology that could take the human factor out of insulin delivery, via a continuous delivery system that lasts months.

Here at *The American Journal of Managed Care*, we are preparing for our third meeting of Patient-Centered Diabetes Care, which we will be presenting in cooperation with Joslin Diabetes Center of Harvard, in downtown Boston, April 16-17, 2015. The agenda will cover clinical, technological, and behavioral aspects of diabetes care, and we encourage you to join us for important discussions that will include:

- The digital path for better adherence
- Community as part of the prescription: social media in diabetes care
- The role of clinicians and diabetes educators in lifestyle management
- Integrated delivery networks and adherence intervention
- Matching patients to the right treatment through personalized medicine
- Weighing the value of novel treatments in diabetes
- Finding the balance in lipid management
- A review of the 2015 Dietary Guidelines
- A debate on the merits of using combination therapy in diabetes care

To register, please visit http://www.ajmc.com/meetings/pcdc15. It's a great time of year to be in Boston, and we look forward to seeing more of you than ever.

Thank you for reading,

Brian Haug,
President, Managed Markets

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.

SP43 *Research continues to find new benefits of a Mediterranean diet. An updated clinical guideline from the American Heart Association and the American Stroke Association states the diet can control blood pressure and prevent first time stroke.*

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Join Us in Boston for Patient-Centered Diabetes Care 2015

Robert A. Gabbay, MD, PhD, FACP

At the Joslin Diabetes Center, we are committed to making the lives of those with diabetes better through world-class research, patient care, and education. We are engaged in activities across the spectrum of diabetes innovation, leveraging our strengths in clinical care, research, and education to address this global epidemic. We continue to export the models for care and education developed here in Boston to share them with others around the world. Over our 116-year history, we have introduced new care models, from the role of the diabetes educator to team-based care to population health to new treatment for complications, such as the discovery of laser photocoagulation for diabetic retinopathy.

It is this commitment to sharing what we know and to engaging others who can aid us in our mission of preventing and treating diabetes and its complications that makes us especially excited to join with *The American Journal of Managed Care* to present **Patient-Centered Diabetes Care 2015**. This year, the third that *AJMC* has presented the conference, it will be held April 16-17, 2015, at the Renaissance Boston Waterfront Hotel.

Past attendees of this meeting or Joslin's Diabetes Innovations conference know why this partnership works so well. A shared goal of these meetings has been to convene stakeholders from across the healthcare spectrum: payers, policy makers, leaders in clinical care and research, diabetes educators, and, of course, patients and their advocates. Patient-Centered Diabetes Care 2015 will continue this tradition, as we will bring together esteemed faculty, both as presenters and participants in panel discussions. The topics will cover the diversity of issues that affect diabetes care. Over 2 days, we will share new findings in clinical research, gain insights into the behavioral issues that affect diabetes treatment, and learn about new technology that could transform care.

Bringing the conference to Boston has allowed us to tap the vast expertise of our faculty at Joslin, and more broadly, at Harvard's programs in public health. We will also be joined by leading payers, educators, and patient advocates. I would like to highlight just a few of the participants who are coming to Boston:

Om P. Ganda, MD, is senior physician and medical director of the Lipid Clinic and chairman of the Clinical Oversight Committee at Joslin. Dr Ganda, who is an associate clinical professor of medicine at Harvard Medical School, will be speaking about new developments in lipid management.

Howard A. Wolpert, MD, is the director of the Joslin Institute for Technology Translation (JITT) and director of Insulin Pump and Continuous Glucose Monitoring programs. Dr Wolpert, who is an associate professor of medicine at Harvard Medical School, will share insights from his award-winning research on how technology can change the landscape of diabetes management.

Frank Hu, MD, MPH, PhD, is a professor of epidemiology and nutrition at the Harvard School of Public Health and is completing service as a member of the 2015 Dietary Guidelines Advisory Committee. Dr Hu, who is director of the epidemiology and genetics core of the Boston Obesity Nutrition Research Center, will discuss the impact of national nutrition policy.

Amy Tenderich, the founder and editor of DiabetesMine™, is one of the nation's most important diabetes patient advocates. She returns to Patient-Centered Diabetes Care this year to discuss the role of social media in the treatment and education of persons with diabetes. Clinicians who are not using social media need to hear from Ms Tenderich and her fellow panelists.

Hope Warshaw, MMSc, RD, CDE, BC-ADM, is the president of Hope Warshaw Associates, LLC, a diabetes and nutrition consultancy and an important force in the use of social media to educate persons with diabetes.

Edmund J. Pezalla, MD, MPH, vice president and national medical director, Pharmacy Policy and Strategy, Aetna Inc, and **Todd Prewitt, MD,** corporate chronic condition medical director for Humana, Inc, are among the representatives from national commercial payers who are taking part in panel discussions. They'll contribute to discussions on the role of integrated delivery networks in promoting adherence and a debate on whether combination therapies are worth the cost.

Of course, this is just the beginning. For clinicians especially, Patient-Centered Diabetes Care 2015 will offer a unique opportunity to interact with key leaders across the healthcare continuum to share innovative approaches to improve the lives of those with diabetes. This meeting will also offer a chance for decision makers in the payer community, for leading patient advocates, and for those who influence healthcare policy to interchange ideas and address the opportunities and challenges of Patient Centered Diabetes Care. I encourage you to join us in Boston.

Dr Gabbay is chief medical officer and senior vice president at the Joslin Diabetes Center, Boston. **EBDM**

> *"Bringing the conference to Boston has allowed us to tap the expertise of faculty at Joslin, and more broadly at Harvard's programs in public health. Also joining us will be leading payers, educators, and patient advocates."*

For Staying Power, Diabetes Interventions May Need a Hands-on Element

Anthony Hagen

It was clear to Kate Lorig, DrPH, immediately that she was dealing with a special case in her type 1 (T1DM) and type 2 diabetes mellitus (T2DM) self-management workshop at the Stanford Patient Education Research Center, where she serves as director. Lorig had asked a female diabetic what sort of a commitment she could make to reduce her sugar intake.

The woman replied that she would eat no more than 2 candy bars a day. While that's not an ideal goal for a diabetic, Lorig didn't bat an eye. "I said 'How certain are you that you'll eat no more than 2 candy bars a day?' "

The woman started to cry. "You understand," she said. "I'm eating 8 candy bars a day. During break, I went out to my car and ate 2 candy bars."

For this particular diabetes patient, Lorig knew no formulaic management plan was going to succeed. The patient needed a solution adapted to her own situation, which a face-to-face encounter was able to uncover.

"She's made a huge commitment," Lorig said. "If I'd given her the lecture on carbohydrates at that point, I'd never have seen her again. It's going for the real, not the ideal."

In battling chronic diseases like T1DM and T2DM outside the hospital, researchers and doctors who spoke with *Evidence-Based Diabetes Management* agreed that intense involvement with patients is the key to success, though it often comes at a high price that cannot be sustained given the current structure of the healthcare reimbursement system.

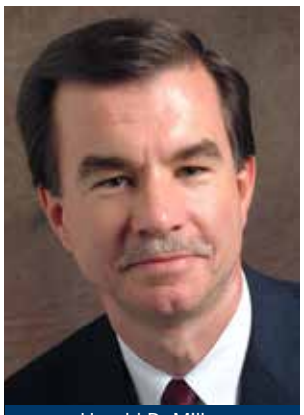
Elizabeth Rula, PhD

Despite calls for value-based care, limitations in the reimbursement system still obstruct successful patient management, said Harold D. Miller, president and CEO of the Center for Healthcare Quality and Payment Reform. Miller served as strategic initiatives consultant for the Pittsburgh regional health initiative from 2006 to 2010, where nurses were sent to the homes of people discharged from the hospital and were empowered to do what they, as nurses, thought was necessary to help the patients adhere to a recovery plan.

The chronic disease management program was a success, though it had to be funded through foundation grants as there was no established payment system under Medicare, Medicaid, or commercial insurance. There were no other standard medical services rev-

enue that could be tapped, Miller said.

"Nurses are trained to be able to help their patients, and the idea was let the nurse figure out what the problems were and what needed to be done about them, rather than being limited to do a specific kind of thing," Miller said. The nurses encountered the same sorts of problems that Lorig sees in the Stanford self-management classes—problems that aren't easily anticipated by a doctor sending a patient home from a hospital or divined by a nurse making a follow-up telephone call.


Harold D. Miller

"One nurse who went to a home found that a patient had been using a nebulizer, and he was dutifully washing it every day according to instructions, but he was putting it wet into a plastic bag, which was a perfect breeding ground for bacteria," Miller said. He added that he was aware of examples from similar programs in other parts of the country, such as a diabetes patient who couldn't see properly to put the needle into his insulin bottle. "It's hard to imagine all of the unique kinds of circumstances like that," he said. "Many patients can't read, can't see, or can't understand, and educational material alone may not solve the problem. They didn't see it or they didn't realize what it meant."

The Pittsburgh project generated more savings in avoidable hospitalizations than the nurse intervention cost, Miller said, but the program only continues today because a local hospital was willing to pay for 1 nurse to continue making house calls. Other studies have shown that well-designed patient education and self-management programs can more than pay for themselves by improving patient outcomes, he said.

Diabetes, as a chronic disease, ranked third in 2011 for the number of Medicaid readmissions (23,700) behind schizophrenia (35,800) and mood disorders (41,600), according to the Healthcare Cost and Utilization Project.[1] CMS has not yet implemented formal readmission reduction targets, though some medical professionals wonder if that isn't imminent, based on the direct medical cost of T1DM and T2DM expenditures, which amounted to $176 billion in 2012, according to a recent study by the American Diabetes Association.[2] Such targets could add more urgency to the quest to have patients take on more responsibility for managing their own health.

"Diabetes is infrequently the primary cause of readmission," said Mary Korytkowski, MD, professor of medicine and interim chief of the Division of Endocrinology at the University of Pittsburgh. "It may eventually be recognized as a contributor to need for readmission, but is not currently a focus of many readmission prevention strategies." Diabetes is often an underlying problem for many hospital admissions and readmissions, such as pneumonia, congestive heart failure, and vascular disease, Korytkowksi said. For this reason, whenever a patient comes into the hospital for what may or may not be a diabetes-related ailment, doctors and nurses need to know about this to allow analysis of the current level of glycemic control, as well as a patient's ability to participate in recommended self-management.


Jason Turi

In a T1DM and T2DM patient education program conducted in Pittsburgh, with results published in late 2013, Korytkowski and her fellow researchers concluded that a course of inpatient education could have positive effects on both short- and long-term patient health outcomes in this patient population. "The ability of patients with diabetes to achieve desired metabolic goals while reducing risk for long-term complications requires education in self-management practices with periodic reinforcement of these principles. For this reason, a program of diabetes self-management education (DSME) is recommended as standard of care for all patients with diabetes," the report stated.[3]

The same report estimated that fewer than 50% of patients receive DSME, which puts them at increased risk for complications and hospitalization. Even so, the growing emphasis on self-management education today is a vast improvement from before, Korytkowski said.

Years ago, Korytkowski said, diabetes classes were held for hospitalized patients once or twice a week. These classes required patient attendance, which was not always realistic in those with acute medical problems. This resulted in poor attendance, she said. But patient education is one of the things competing for health workers' attention and, as a result, it suffers the fate of many other prioritized needs, Korytkowski said. "There's so much attention now on limiting length of stay and just taking care of the issue that brought them into the hospital. So, say they have pneumonia: you treat the pneumonia, but the fact that their blood sugar is off just doesn't rise to the surface. The pace of things just doesn't allow for all of these things that brought them to the hospital to be addressed."


Kate Lorig, DrPH

A multi-year study on an Australian population of chronic heart disease and T1DM and T2DM patients published in April 2013[4] weighed the value of repeated phone contact through the My Health Guardian (MHG) health maintenance program, which included follow-up with patients after discharge. "MHG proved to be an effective means to reduce the likelihood and duration of hospitalizations for individuals with diabetes and heart disease," authors of the study wrote. "In this study, the MHG program demonstrated a consistent effect; treatment group members had reduced admissions, readmissions, and ALOS (average length of stay) relative to comparison group members....Furthermore, the magnitude of effect increased over time, demonstrating the importance of a sustained program for maximizing impact."

While other researchers contend that face-to-face contact with patients outside the hospital is often essential to tailor diabetes management to individual situations, study coauthor Elizabeth Rula, PhD, said, telephonic management has a place in managed healthcare. "Diabetes is one of the conditions that is known to be very susceptible to improvement as a result of these programs," said Rula, who is executive director and principal investigator at the *Healthways* Center for Health Research in Tennessee. Healthways is the provider of the MHG program that was studied.

"We identified people who had recently been discharged or hospitalized, and tried to reach out to them," Rula said. "That is a really critical point in time—you might call it a teachable moment—in terms of when someone is acutely aware their health is not optimally managed. So at that point, they can be amenable to the program and changes in how they are managing."

In a prior study of telephonic follow-up for admitted patients with chronic conditions, nurse-delivered calls occurring within 14 days after discharge were associated with a 23% decrease in readmissions. From her work on this study, Rula saw the importance of timely follow-up, "because most readmissions occurred within 2 weeks of discharge, and a third within 1 week. Delays in identifying or reaching patients once they return home create missed opportunities to prevent a return to the hospital."[5]

One of the barriers to the Australian program, however, was the limited amount of patient medical history information available, contrary to what US medical personnel generally have at their disposal, Rula said. Knowing more about patients' medical history enables a more targeted approach in the telephonic program, she said.

"Typically we are able to model who is at highest risk for readmission, and reaching out to them is not a one-way push for information," Rula said. "Here in the States, we often have access to a more robust picture of that person's prior claims. When we're working with health systems, we can actually get in up front and do an assessment of patients while they are in the hospital and start working with them at that point in time to allow early identification of that person's needs and barriers that could result in a readmission."

She said the potential of working with a patient before and after their care transition "is shown in our recent evaluation of the full model where we were able to initiate needs assessment and discharge planning in the hospital, which is then supported by telephonic follow-up."

The success of the multiple phone call approach in the MHG study was not replicated in a study published this fall in *Diabetes Care*, where researchers found that a single scripted phone call to T2DM patients was not successful in getting them to adhere to the use of a new medication.[6] A stated goal was to test whether this relatively inexpensive form of intervention would increase medication adherence, but the authors concluded: "This low-intensity intervention did not significantly improve medication adherence or control of glucose, blood pressure, or low-density lipoprotein cholesterol. Wide use of this strategy does not appear to be warranted; alternative approaches to identify and improve medication adherence and persistence are needed."

Some believe the money spent on telephonic management is not wisely invested and actually diverts funds from more productive patient management and education initiatives. In Camden, New Jersey, the Camden Coalition of Healthcare Providers' (CCHP) Care Management Program, Link2Care, has claimed a significant reduction in patient readmissions and nonemergent use of hospital emergency departments via the use of

health teams who track patients from the hospital setting back into the community and provide support services that ensure that even patients' housing needs are addressed.

Targeting high-volume users of the health system, "A team of nurses, social workers, community health workers, and health coaches, supported by data of healthcare utilization, perform home visits, accompany patients to doctor visits, and help patients enroll in social-service programs," according to program literature.

In Camden, where per capita income is significantly lower than in the rest of New Jersey, researchers were finding patients who not only didn't have insulin, "They didn't have food, their electricity was getting turned off, and they were significantly depressed," all factors that contributed to their inability to manage their health conditions more successfully, said Jason Turi, associate clinical director of the CCHP.

Such patients were among a population of 20% of hospital users who accounted for 90% of costs at 3 Camden hospital systems from 2002-2007. The team approach to care management was "found to improve health outcomes [and] decrease utilization of emergency and inpatient services and costs for a cohort of 36 'high utilizers' from $1.2 million monthly to $534,000 monthly, a saving of 56% over 5 years."[7]

"Part of the sustainability strategy for operations like ours and around the country is to reroute money away from telephonic management and into community-based operations," because the belief is that community-based programs work better, Turi said. That is accomplished by working at the policy level, "actually getting to where care management dollars are going for publicly insured folks, especially Medicaid, to working here in New Jersey with our funders and with the Medicaid office to start rethinking what it means to do case management for complex patients."

The program is currently the focus of a Massachusetts Institute of Technology proof-of-concept study that Turi believes will confirm what he considers the legitimacy of the approach and make funding easier to obtain. The program has already won a pay-for-performance contract from UnitedHealthcare, which administers Medicaid payments in New Jersey. "This is actually not a grant," Turi said, "which is great. They pay us to service some of their more complex patients in Camden." **EBDM**

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CLINICAL GUIDELINE

Updated Guideline, Research Favor Mediterranean Diet to Control Blood Pressure, Prevent First-Time Stroke

Mary K. Caffrey

The American Heart Association (AHA) and American Stroke Association (ASA) released an updated guideline last fall recommending the Mediterranean or DASH-style diet (Dietary Approaches to Stop Hypertension) as a way to lower the risk of first-time stroke.[1] The guideline update, appearing in the journal *Stroke*, is just the latest endorsement for consuming a diet rich in fruits, vegetables, whole grains, and nuts, as well as increasing physical activity and not smoking to improve cardiovascular health, control weight, and prevent or reduce the effects of diabetes.[2]

Recent studies continue to affirm the positive effects of the Mediterranean diet on cardiometabolic and overall health. Among the results:

- Lau, Wong, et al published a study the same day as the new guideline in the *American Journal of Hypertension*, which tracked a group of patients who already had coronary artery disease. Those who more closely followed the Mediterranean diet were less likely to experience spikes in blood pressure or suffer strokes than those who did not follow the diet closely.[3]
- A novel study published in December 2014 in the *British Medical Journal* found that in a randomized controlled trial, patients with reduced sodium intake were less likely to have headaches than those with a normal diet.[4]

The AHA/ASA guideline update was based on a study led by James Meschia, MD, professor and chairman of neurology at the Mayo Clinic, Jacksonville, Florida. "We have a huge opportunity to improve how we prevent new strokes, because risk factors that can be changed or controlled—especially high blood pressure—account for 90% of strokes," he said.[5]

The update included the following specific recommendations:

- Eat a Mediterranean or DASH-style diet, supplemented with nuts.
- Monitor high blood pressure at home with a cuff device.
- Keep prehypertension from becoming high blood pressure by making lifestyle changes such as getting more physical activity, eating a healthy diet, and managing weight.
- Reduce the amount of sodium intake; sodium is found mostly in salt.
- Visit your healthcare provider annually for blood pressure evaluation.[1]

The update also specifically addressed the issue of medication adherence, which is a significant problem in treating diabetes and high blood pressure. Patients whose medication isn't working or is causing intolerable side effects shouldn't stop taking it—they should ask their doctor for something else, the guideline states.[1]

The AHA/ASA update specifically addressed medication adherence, which is a problem in treating diabetes and blood pressure.

The AHA/ASA guideline describes the Mediterranean-style or DASH-style diet as emphasizing vegetables, whole grains, legumes, nuts, seeds, poultry, and fish. Both are limited in red meat and foods containing saturated fats, which are mostly found in animal-based products such as meat, butter, cheese, and full-fat dairy. According to a statement from the AHA, Mediterranean-style diets are generally low in dairy products and DASH-style diets emphasize low-fat dairy products.[5]

Finally, the AHA statement warns against smoking, especially among women taking oral contraceptives, and states that avoiding secondhand smoke lowers stroke and heart attack risks. **EBDM**

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Preventing Beta Cell Destruction in T1DM

Surabhi Dangi-Garimella, PhD

While diabetes continues to be a major global health concern, disease management, not cure, remains the steadfast goal. According to the 2014 National Diabetes Statistics Report from the CDC, a steady increase in the number of diabetic patients has been observed since 2010: 29.1 million Americans were estimated to have diabetes in 2012, up from 25.8 million in 2010, including more than 8 million who were undiagnosed. Hyperglycemia, however, is not a health condition managed in isolation; in addition to serious complications associated with disease progression (eg, microvascular disease, blindness, and lack of wound healing), diabetes also increases one's susceptibility to cardiovascular disease, dyslipidemia, stroke, and kidney disease. A tremendous influence on the overall health of an individual, diabetes-associated healthcare costs amount in the billions. The cost in the United States alone was estimated at $245 billion in 2012, and 30% of the expenses were calculated as being indirect, such as those due to loss of productivity.[1]

Anath Shalev, MD

Type 1 diabetes mellitus (T1DM), previously known as juvenile diabetes, is diagnosed in only 5% of people with hyperglycemia.[2] An autoimmune disorder that results in the immune-mediated destruction of the pancreatic β cells that produce insulin, T1DM can affect both children and young adults, resulting in a lifetime of insulin therapy.

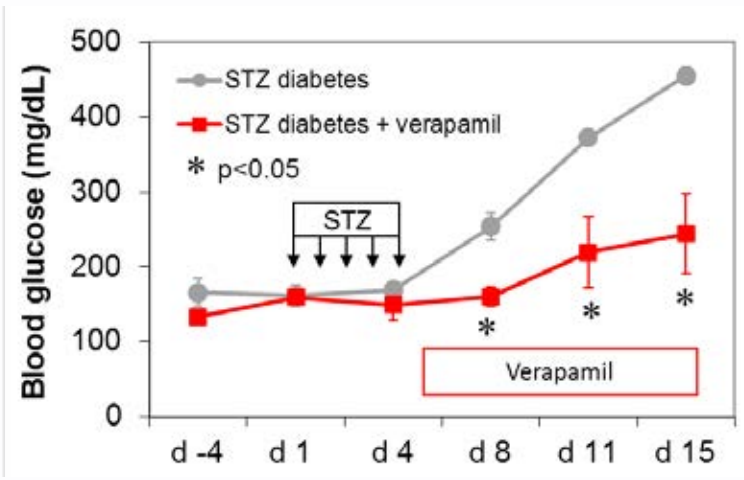
ALTERNATIVES TO INSULIN

Several out-of-the-box approaches are being evaluated in T1DM patients to save them the misery of everyday insulin treatment. One such approach is transplanting these patients with functional insulin-producing β cells that have been differentiated from human pluripotent stem cells (hPSCs). A collaborative study between the Harvard Stem Cell Institute and the Diabetes Center of Excellence at the University of Massachusetts generated functional human β cells from hPSCs in vitro without any genetic alterations of the cells. The β cells, which were generated following sequential differentiation resulting from high-glucose challenges, were structurally and functionally similar to pancreatic β cells. Mice transplanted with these cells could secrete insulin and reduce hyperglycemia.[3]

Another approach has been to regulate a person's immune system to suppress the autoimmune response generated in individuals with T1DM, the hypothesis being that a personalized approach to modulating the immune system could cure patients. While generalized immune suppression is not a feasible option—considering the associated adverse effects—procedures such as autologous hematopoietic stem cell therapy could prove useful. Clinical immune interventions have been conducted, but immune-modulators such as rituximab and otelixizumab showed functional variability based on age and ethnicity.[4]

Vaccination with HLA-binding peptide epitopes is another option, though several challenges remain, including a person's HLA haplotype, defining the route of administration, and the dose and frequency of administration. Trials examining the efficacy of cell therapy with FOXP3$^+$ T_{REG} cells to halt T1DM progression are presenting encouraging results in preliminary studies. However, the specificity of the FOXP3$^+$ T_{REG} cells to selectively suppress islet autoimmunity, as well as stability of their cells, remains questionable.[4]

FIGURE. Verapamil Reduces Blood Glucose in a Diabetes Mouse Model



SOURCE: http://www.uab.edu/medicine/diabetes/new-clinical-trial. Accessed January 12, 2014.

REPURPOSING THE CALCIUM CHANNEL BLOCKER VERAPAMIL

In their attempt to find a cure for T1DM and to help rid patients of their daily insulin dose, investigators at the University of Alabama at Birmingham (UAB) have designed a clinical trial to evaluate the blood pressure medication verapamil for use in T1DM.[5] To be initiated early this year, the trial, funded by a multi-million dollar grant from the Juvenile Diabetes Research Foundation, is based on preliminary evidence from a mouse model, which showed that the commonly used blood pressure medication could completely reverse diabetes in mice.[6]

Research conducted in the laboratory of Anath Shalev, MD, director of UAB's Comprehensive Diabetes Center, found that administering oral verapamil could prevent β-cell death in mice with T1DM. How? The authors found that verapamil repressed the expression of thioredoxin-interacting protein (TXNIP), a gene whose glucose-regulated expression is induced in the islets of diabetic individuals, resulting in β-cell death.[6] TXNIP also induces the expression of IL-1β, a cytokine that promotes T1DM. Following their discovery that verapamil can inhibit the expression of TXNIP,[7] Shalev's research team evaluated the drug in vitro in pancreatic β cells, and in vivo in mice, and found that verapamil-mediated downregulation of TXNIP prevented β-cell apoptosis, improved β-cell survival and function, and rescued mice from diabetes. Importantly, verapamil could regulate TXNIP expression only in the presence of elevated glucose levels, which offsets any unwanted side effects due to excessive reduction of TXNIP below physiological levels.[6]

THE VERAPAMIL TRIAL

The trial aims to enroll 52 people, 19 to 45 years of age, within 3 months of being diagnosed with T1DM. These patients will be initiated on a placebo or verapamil while on their insulin pump therapy, and blood glucose will be monitored using a continuous glucose monitoring system.[5] In an e-mail, Shalev informed *Evidence-Based Diabetes Management* that the trial, which has already been initiated, will continue to enroll adults within 3 months of being newly diagnosed with T1DM, until spring 2016.

The current trial will follow patients for a period of 1 year after initiating verapamil. However, Shalev informed *EBDM* that funding permitted, encouraging results from the current trial would be followed-up with a longer-term trial to observe more sustained effects of verapamil. "We definitely would like to conduct a longer-term trial, as 1-year may indeed be rather short to see the full extent of the effects in humans. At that point, we would also like to expand our inclusion criteria to allow patients with slightly longer disease duration to participate," wrote Shalev.

Although it's early to predict verapamil adoption in practice, Shalev hopes it will be, considering that the molecule has already been used in clinic for other indications for 30 years. "So, adaptation into clinical practice would only require official repurposing. At least until more specific strategies are being developed and tested down the road, it would provide a unique approach trying to enhance the patient's own beta cell mass and insulin production," Shalev anticipates.

Additional information on the project can be found at http://www.uab.edu/medicine/diabetes/new-clinical-trial.

EBDM

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A Look Beyond Findings on Telephone Intervention Reveals Why Having Data Matters

Mary K. Caffrey

Last fall, when the journal *Diabetes Care* published results of a large "pragmatic randomized trial" that measured how well a basic telephone intervention worked to promote medication adherence, the results on their face appeared bleak.


Patrick J. O'Connor, MD, MA, MPH

In the study, 2378 adults were selected to receive a new class of medication for treating elevated levels of glycated hemoglobin (A1C) ≥8% (64 mmol/mol), blood pressure ≥140/90 mmHg, or low-density lipoprotein (LDL) cholesterol ≥100 mg/dL. They were assigned randomly to intervention and usual care groups. Everyone in the first group received 1 scripted phone call from a diabetes educator or clinical pharmacist to gauge how many had picked up a new prescription the first time, picked up subsequent prescriptions in a 3-month period, and achieved improvements in blood pressure, A1C, and LDL cholesterol levels.[1]

Researchers found the outreach effort made no difference in overall adherence, in medication persistence, or in intermediate health outcomes. But rather than be disappointed with these results, lead author Patrick J. O'Connor, MD, MA, MPH, and senior clinical investigator for HealthPartners, now knows where the healthcare system or accountable care organizations (ACOs) should *not* direct resources. When the patients who were receiving the intervention were contacted 2 to 3 weeks after getting their prescription, "80% of them had already filled it," he said in an interview with *Evidence-Based Diabetes Management*, leaving only 20% who could potentially be affected by the outreach.

Based on the results, O'Connor said, it makes little sense to "burn your money to make calls to everybody with a prescription." Instead, he compared results of his study with those of Derose and colleagues published in early 2013. That study, published in the *Journal of the American Medical Association Internal Medicine*, reported an effort by Kaiser Permanente Southern California to target only those patients who had not filled a statin prescription, using automated phone calls and follow-up letters.[2] The study found that 42.3% of patients receiving the intervention filled their statin within 2 weeks, compared with only 26% of patients in a control group.[2]

O'Connor said comparing the 2 sets of data shows that having access to real-time data and the ability to use it to target only those patients who have not picked up their prescriptions makes all the difference in a successful effort to improve medication adherence. Despite their different results, authors of both studies agreed on their point.

"There's an important lesson here," O'Connor told *EBDM*. Broad-based outreach is probably not cost-effective unless health plans and pharmacies can integrate information systems to the point that those designing outreach programs can target patients who are considered "the late fillers." Fill data, he noted, comes from the claims data and the electronic medical record. An integrated system like Kaiser's, he said, is likely still the exception. "When health information exchanges are fully operative and in place, you can integrate claims data with the prescribing data," he said. "You have to be pretty close to real time for this to work."

On the plus side, O'Connor said, Derose and colleagues found that automated phone calls were fairly effective, which suggested that if the investment is made to integrate the real-time claims data with the outreach, the cost of making the outreach itself can be controlled.

"MINIMALLY DISRUPTIVE MEDICINE"

Medication adherence is a huge challenge in diabetes care, O'Connor said, and one reason is the sheer number of pills that some patients end up taking after a while. Research is starting to address this phenomenon, he added, which is likely to become a bigger issue with the emergence of guidelines that reward or punish ACOs based on how well their patients do in achieving clinical targets for diabetes.

Depending on the patient, O'Connor said, it may not make sense to pile on more medicine if 1 target is just a little off, if it means more side effects and costs for a patient who is otherwise making progress. Rather, it's best to focus on the target that presents the most risk—and which will offer the patient the greatest benefit if he or she can make improvement. O'Connor called this the principle of "minimally disruptive medicine," which he said has gained notice in recent years. Two recent qualitative studies involving this concept interviewed dozens of patients with multiple chronic conditions, seeking to understand their challenges and build frameworks for improving their care.[3,4]

"Most patients (with diabetes) only have 1 or 2 things out of goal," he said. Giving patients targets they can achieve is more likely to bring success, O'Connor added. **EBDM**

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Liraglutide Approved Under New Name to Treat Obesity

Mary K. Caffrey

On December 23, 2014, the FDA approved liraglutide, under the name Saxenda, to treat obesity, after having previously approved it under the name Victoza to treat type 2 diabetes mellitus (T2DM).

As Saxenda, the glucagon-like peptide-1 (GLP-1) receptor agonist will be approved for adults with a body mass index (BMI) of 30 or higher, or for adults with a BMI of 27 or higher plus at least 1 other comorbidity, such as T2DM or high cholesterol. The FDA specifically warned against patients taking any other GLP-1 drugs along with Saxenda, including Victoza.[1]

While the 2 drugs contain the same active ingredient, the approved dose for Saxenda is higher, at 3 mg, than for Victoza, at 1.8 mg.[1]

The approval for Saxenda (liraglutide [rDNA origin] injection) is based on results from a clinical trial that enrolled patients without diabetes, which showed that patients had an average weight loss of 4.5% from baseline compared with those receiving placebo for 1 year. In the trial, 62% of patients treated with Saxenda lost at least 5% of their body weight compared with 34% of those treated with placebo.

In another clinical trial, at the 1-year mark, patients with T2DM had an average weight loss of 3.7% from baseline compared with those receiving placebo. In this trial, 49% of patients treated with Saxenda lost at least 5% of their body weight compared with 16% of patients treated with placebo.


Mads Krogsgaard Thomsen

In a statement, the FDA said patients who receive Saxenda should be evaluated after 16 weeks to see if the drug is working, and the drug should be stopped if a patient has not lost at least 4% of baseline body weight.

Saxenda has a boxed warning stating that tumors of the thyroid gland have been observed in studies with rodents, but that it is unknown whether the drug causes thyroid tumors in humans. Persons with a family history of medullary thyroid carcinoma or those with multiple endocrine neoplasia syndrome type 2 should not take the drug. The FDA also ordered several post marketing studies for Saxenda.

Common side effects were nausea, diarrhea, constipation, vomiting, low blood sugar, and decreased appetite.[1]

In a statement, manufacturer Novo Nordisk said Saxenda will be launched in the first half of 2015. "Many people suffer from comorbidities. Saxenda has the potential to help some of those people achieve and maintain a clinically significant weight loss and improve their weight-related comorbidities," said Mads Krogssgaard Thomsen, executive vice president and chief science officer.[2] **EBDM**

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LEGISLATIVE UPDATE

Getting CGM Covered by Medicare Still on the Agenda

Mary K. Caffrey

The 113th Congress adjourned without passing an important agenda item of diabetes advocacy groups: getting Medicare to cover continuous glucose monitors, or CGM technology. Yet, supporters of this policy change, especially the Juvenile Diabetes Research Foundation (JDRF), are hopeful it will pass in the session of Congress that starts this month, based on the support the measure has received, despite being advanced quite late in the last session.

JDRF has taken the lead to address a problem that has grown worse each year, as more persons with type 1 diabetes mellitus (T1DM) live to retirement and rely on Medicare for their health coverage. After years of living full lives, thanks to improving technology often covered by commercial insurance, these patients find that Medicare will not cover the devices that have given them the ability to monitor their blood sugar in real time.[1]

After years of being accustomed to finely tuned adjustments to insulin intake that prevented episodes of hypoglycemia or hyperglycemia, seniors who retire often lose access to CGM technology, only to see their hospitalization rates rise. Some approaching retirement live in fear of what is to come.[1] Unfortunately, the legislation had a lot working against it. First, it was a spending measure, and it was never scored by the Congressional Budget Office. Second, it was not introduced until the summer, when every member of the House of Representatives and one-third of the Senate was busy campaigning for reelection. Yet, as JDRF's Christopher Rucas noted shortly after Congress adjourned, it still gained 41 co-sponsors in the House (19 Republicans and 22 Democrats) and 16 in the Senate (6 Republicans and 10 Democrats).

"Our champions in the House and Senate will reintroduce the Medicare CGM Access Act when the new Congress convenes in January," Rucas said in a statement to *Evidence-Based Diabetes Management*.

The bipartisan support bodes well for the ability of the JDRF and other diabetes advocates to eventually gain coverage for CGM. The chief reason for the late introduction is that groups had been working with CMS on an administrative solution for Medicare coverage, and the legislative route was taken after those efforts stalled. Published reports in online resources for persons with diabetes, such as *DiabetesMine*, recount unsuccessful efforts to convince CMS officials that CGM technology is not simply more convenient; it's essential for patient safety.[2] Rucas said as 2015 begins, JDRF will pursue both legislative and administrative strategies to get CGM technology broadly covered by Medicare for seniors who have T1DM.

Advocates frequently cite a 2011 study from *The American Journal of Managed Care* in making their case. That study found that every incident of hypoglycemia that results in a trip to the emergency department costs $17,564, and many of these incidents could be avoided with more widespread use of CGM technology.[3] **EBDM**

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Risk of Thyroid C-cell Tumors: Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors (eg, a mass in the neck, dysphasia, dyspnea, persistent hoarseness). Patients with elevated serum calcitonin (if measured) and patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation.

Pancreatitis: Has been reported in clinical trials. Observe patients for signs and symptoms including persistent severe abdominal pain. If pancreatitis is suspected discontinue Trulicity promptly. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapy.

Please see Important Safety Information continued on following page.

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Important Safety Information, continued

Hypoglycemia: The risk of hypoglycemia is increased when Trulicity is used in combination with insulin secretagogues (eg, sulfonylureas) or insulin. Patients may require a lower dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia.

Hypersensitivity Reactions: Systemic reactions were observed in clinical trials in patients receiving Trulicity. Instruct patients who experience symptoms to discontinue Trulicity and promptly seek medical advice.

Renal Impairment: In patients treated with GLP-1 RAs there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, sometimes requiring hemodialysis. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. In patients with renal impairment, use caution when initiating or escalating doses of Trulicity and monitor renal function in patients experiencing severe adverse gastrointestinal reactions.

Severe Gastrointestinal Disease: Use of Trulicity may be associated with gastrointestinal adverse reactions, sometimes severe. Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

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

The most common adverse reactions reported in ≥5% of Trulicity-treated patients in placebo-controlled trials (placebo, Trulicity 0.75 mg and 1.5 mg) were nausea (5.3%, 12.4%, 21.1%), diarrhea (6.7%, 8.9%, 12.6%), vomiting (2.3%, 6.0%, 12.7%), abdominal pain (4.9%, 6.5%, 9.4%), decreased appetite (1.6%, 4.9%, 8.6%), dyspepsia (2.3%, 4.1%, 5.8%), and fatigue (2.6%, 4.2%, 5.6%).

Gastric emptying is slowed by Trulicity, which may impact absorption of concomitantly administered oral medications. Use caution when oral medications are used with Trulicity. Drug levels of oral medications with a narrow therapeutic index should be adequately monitored when concomitantly administered with Trulicity. In clinical pharmacology studies, Trulicity did not affect the absorption of the tested, orally administered medications to a clinically relevant degree.

Pregnancy: There are no adequate and well-controlled studies of Trulicity in pregnant women. Use only if potential benefit outweighs potential risk to fetus.

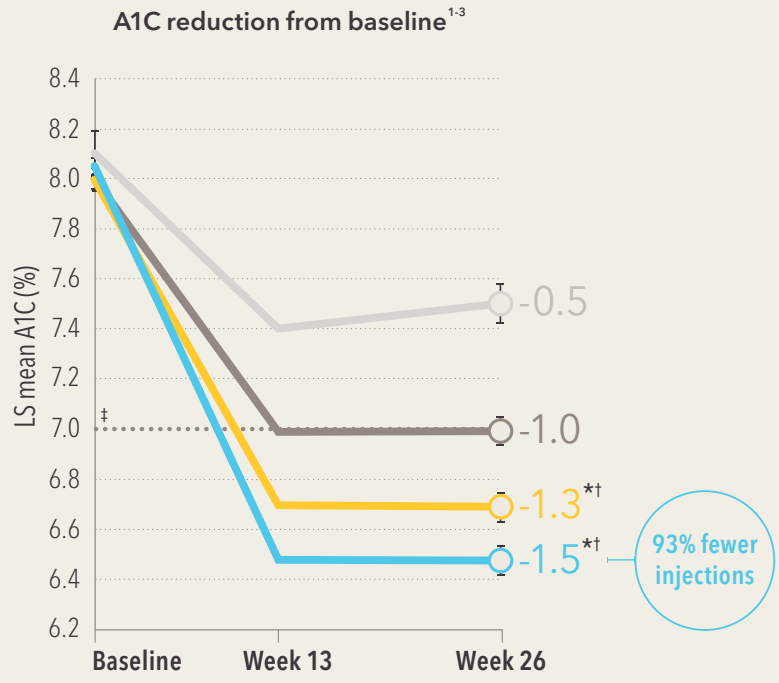
Nursing Mothers: It is not known whether Trulicity is excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue Trulicity taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of Trulicity have not been established and use is not recommended in patients less than 18 years of age.

Please see Brief Summary of Full Prescribing Information including Boxed Warning about possible thyroid tumors including thyroid cancer on following pages. Please see Instructions for Use included with the pen.

DG HCP ISI 18SEP2014

Once-weekly Trulicity showed significant A1C reduction[1]



- **Placebo** (n=141; Baseline A1C: 8.1%)
- **Byetta® (10 mcg BID)** (n=276; Baseline A1C: 8.1%) **Injections: ~730/year**
- **Trulicity™ (0.75 mg)** (n=280; Baseline A1C: 8.1%) **Injections: ~52/year**
- **Trulicity™ (1.5 mg)** (n=279; Baseline A1C: 8.1%) **Injections: ~52/year**

Data represent least-squares mean ± standard error.

* Multiplicity-adjusted 1-sided *P* value <.025 for superiority of Trulicity vs Byetta for A1C.

† Multiplicity-adjusted 1-sided *P* value <.001 for superiority of Trulicity vs placebo for A1C. Mixed model repeated measures analysis. After 26 weeks, placebo-treated patients were switched in a blinded fashion to Trulicity 1.5 mg or Trulicity 0.75 mg.

‡ American Diabetes Association recommended target goal. Treatment should be individualized.[4]

- 52-week, randomized, placebo-controlled phase 3 study (open-label assignment to Byetta or blinded assignment to Trulicity or placebo) of adult patients with type 2 diabetes treated with maximally tolerated metformin (≥1500 mg/day) and Actos® (up to 45 mg/day)
- Primary objective was to demonstrate superiority of Trulicity 1.5 mg vs placebo on change in A1C from baseline at 26 weeks (-1.5% vs -0.5%, respectively; difference of -1.1%; 95% CI [-1.2, -0.9]; multiplicity-adjusted 1-sided *P* value <.001; analysis of covariance using last observation carried forward); primary objective met

References

1. Trulicity [Prescribing Information]. Indianapolis, IN: Lilly USA, LLC; 2014.
2. Data on file, Lilly USA, LLC. TRU20140910A.
3. Data on file, Lilly USA, LLC. TRU20140919C.
4. American Diabetes Association. Standards of medical care in diabetes–2014. *Diabetes Care*. 2014;37(Suppl 1):S14-S80.

trulicity™

dulaglutide injection once weekly

0.75 mg/0.5 mL, 1.5 mg/0.5 mL

Trulicity™

(dulaglutide)

Brief Summary: Consult the package insert for complete prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS

- **In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies.**
- **Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with Trulicity. Counsel regarding the risk factors and symptoms of thyroid tumors.**

INDICATIONS AND USAGE

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

Limitations of Use:
Not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise. Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. It is not a substitute for insulin. Has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. Not recommended in patients with pre-existing severe gastrointestinal disease. The concurrent use of Trulicity and basal insulin has not been studied.

CONTRAINDICATIONS

Do not use in patients with a personal or family history of MTC or in patients with MEN 2. Do not use in patients with a prior serious hypersensitivity reaction to dulaglutide or to any of the product components.

WARNINGS AND PRECAUTIONS

Risk of Thyroid C-cell Tumors: In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. Glucagon-like peptide (GLP-1) receptor agonists have induced thyroid C-cell adenomas and carcinomas in mice and rats at clinically relevant exposures. It is unknown whether Trulicity will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of this signal could not be determined from the clinical or nonclinical studies. One case of MTC was reported in a patient treated with Trulicity. This patient had pretreatment calcitonin levels approximately 8 times the upper limit of normal (ULN). Trulicity is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the risk for MTC with the use of Trulicity and inform them of symptoms of thyroid tumors (eg, a mass in the neck, dysphagia, dyspnea, persistent hoarseness). The role of serum calcitonin monitoring or thyroid ultrasound monitoring for the purpose of early detection of MTC in patients treated with Trulicity is unknown. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin as a screening test for MTC and a high background incidence of thyroid disease. Very elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. Patients with thyroid nodules noted on physical examination or neck imaging should also be referred to an endocrinologist for further evaluation.

Pancreatitis: In Phase 2 and Phase 3 clinical studies, 12 (3.4 cases per 1000 patient years) pancreatitis-related adverse reactions were reported in patients exposed to Trulicity versus 3 in non-incretin comparators (2.7 cases per 1000 patient years). An analysis of adjudicated events revealed 5 cases of confirmed pancreatitis in patients exposed to Trulicity (1.4 cases per 1000 patient years) versus 1 case in non-incretin comparators (0.88 cases per 1000 patient years). After initiation of Trulicity, observe patients carefully for signs and symptoms of pancreatitis, including persistent severe abdominal pain. If pancreatitis is suspected, promptly discontinue Trulicity. If pancreatitis is confirmed, Trulicity should not be restarted. Trulicity has not been evaluated in patients with a prior history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: The risk of hypoglycemia is increased when Trulicity is used in combination with insulin secretagogues (eg, sulfonylureas) or insulin. Patients may require a lower dose of sulfonylurea or insulin to reduce the risk of hypoglycemia.

Hypersensitivity Reactions: Systemic hypersensitivity reactions were observed in patients receiving Trulicity in clinical trials. If a hypersensitivity reaction occurs, the patient should discontinue Trulicity and promptly seek medical advice.

Renal Impairment: In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Because these reactions may worsen renal failure, use caution when initiating or escalating doses of Trulicity in patients with renal impairment. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.

Severe Gastrointestinal Disease: Use of Trulicity may be associated with gastrointestinal adverse reactions, sometimes severe. Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

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

ADVERSE REACTIONS

Clinical Studies Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Pool of Placebo-controlled Trials:

These data reflect exposure of 1670 patients to Trulicity and a mean duration of exposure to Trulicity of 23.8 weeks. Across the treatment arms, the mean age of patients was 56 years, 1% were 75 years or older and 53% were male. The population in these studies was 69% White, 7% Black or African American, 13% Asian; 30% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8.0 years and had a mean HbA1c of 8.0%. At baseline, 2.5% of the population reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60mL/min/1.73 m^2) in 96.0% of the pooled study populations.

Adverse Reactions in Placebo-Controlled Trials Reported in ≥5% of Trulicity-Treated Patients: Placebo (N=568), Trulicity 0.75mg (N=836), Trulicity 1.5 mg (N=834) (listed as placebo, 0.75 mg, 1.5 mg) nausea (5.3%, 12.4%, 21.1%), diarrhea[a] (6.7%, 8.9%, 12.6%), vomiting[b] (2.3%, 6.0%, 12.7%), abdominal pain[c] (4.9%, 6.5%, 9.4%), decreased appetite (1.6%, 4.9%, 8.6%), dyspepsia (2.3%, 4.1%, 5.8%), fatigue[d] (2.6%, 4.2%, 5.6%). ([a] Includes diarrhea, fecal volume increased, frequent bowel movements. [b] Includes retching, vomiting, vomiting projectile. [c] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, gastrointestinal pain. [d] Includes fatigue, asthenia, malaise.) Note: Percentages reflect the number of patients that reported at least 1 treatment-emergent occurrence of the adverse reaction. Gastrointestinal Adverse Reactions: In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving Trulicity than placebo (placebo 21.3%, 0.75 mg 31.6%,1.5 mg 41.0%). More patients receiving Trulicity 0.75 mg (1.3%) and Trulicity 1.5 mg (3.5%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.2%). Investigators graded the severity of gastrointestinal adverse reactions occurring on 0.75 mg and 1.5 mg of Trulicity as "mild" in 58% and 48% of cases, respectively, "moderate" in 35% and 43% of cases, respectively, or "severe" in 7% and 11% of cases, respectively. In addition to the adverse reactions ≥5% listed above, the following adverse reactions were reported more frequently in Trulicity-treated patients than placebo (frequencies listed, respectively, as: placebo; 0.75 mg; 1.5 mg): constipation (0.7%; 3.9%; 3.7%), flatulence (1.4%; 1.4%; 3.4%), abdominal distension (0.7%; 2.9%; 2.3%), gastroesophageal reflux disease (0.5%; 1.7%; 2.0%), and eructation (0.2%; 0.6%; 1.6%).

Pool of Placebo- and Active-Controlled Trials:

The occurrence of adverse reactions was also evaluated in a larger pool of patients with type 2 diabetes participating in 6 placebo- and active-controlled trials evaluating the use of Trulicity as monotherapy and add-on therapy to oral medications or insulin. In this pool, a total of 3342 patients with type 2 diabetes were treated with Trulicity for a mean duration 52 weeks. The mean age of patients was 56 years, 2% were 75 years or older and 51% were male. The population in these studies was 71% White, 7% Black or African American, 11% Asian; 32% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8.2 years and had a mean HbA1c of 7.6-8.5%. At baseline, 5.2% of the population reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60 ml/min/1.73 m^2) in 95.7% of the Trulicity population. In the pool of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed as ≥5% above.

Other Adverse Reactions:

Hypoglycemia: **Incidence (%) of Documented Symptomatic (≤70 mg/dL Glucose Threshold) and Severe Hypoglycemia in Placebo-Controlled Trials:** Add-on to Metformin at 26 weeks, Placebo (N=177), Trulicity 0.75 mg (N=302), Trulicity 1.5 mg (N=304), Documented symptomatic: Placebo: 1.1%, 0.75 mg: 2.6%, 1.5 mg: 5.6%; Severe: all 0. Add-on to Metformin + Pioglitazone at 26 weeks, Placebo (N=141), TRULICITY 0.75 mg (N=280), Trulicity 1.5 mg (N=279), Documented symptomatic: Placebo: 1.4%, 0.75 mg: 4.6%, 1.5 mg: 5.0%; Severe: all 0. Hypoglycemia was more frequent when Trulicity was used in combination with a sulfonylurea or insulin. Documented symptomatic hypoglycemia occurred in 39% and 40% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with a sulfonylurea. Severe hypoglycemia occurred in 0% and 0.7% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with a sulfonylurea. Documented symptomatic hypoglycemia occurred in 85% and 80% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with prandial insulin. Severe hypoglycemia occurred in 2.4% and 3.4% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with prandial insulin. Heart Rate Increase and Tachycardia Related Adverse Reactions: Trulicity 0.75 mg and 1.5 mg resulted in a mean increase in heart rate (HR) of 2-4 beats per minute (bpm). The long-term clinical effects of the increase in HR have not been established. Adverse reactions of sinus tachycardia were reported more frequently in patients exposed to Trulicity. Sinus tachycardia was reported in 3.0%, 2.8%, and 5.6% of patient treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Persistence of sinus tachycardia (reported at more than 2 visits) was reported in 0.2%, 0.4% and 1.6% of patients treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Episodes of sinus tachycardia, associated with a concomitant increase from baseline in heart rate of ≥15 beats per minute, were reported in 0.7%, 1.3% and 2.2% of patient treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Immunogenicity: Across four Phase 2 and five Phase 3 clinical studies, 64 (1.6%) TRULICITY-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in Trulicity (ie, dulaglutide). Of the 64 dulaglutide-treated patients that developed dulaglutide ADAs, 34 patients (0.9% of the overall population) had dulaglutide-neutralizing antibodies, and 36 patients (0.9% of the overall population) developed antibodies against native GLP-1. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to dulaglutide cannot be directly compared with the incidence of antibodies of other products. Hypersensitivity: Systemic hypersensitivity adverse reactions sometimes severe (eg, severe urticaria, systemic rash, facial edema, lip swelling) occurred in 0.5% of patients on Trulicity in the four Phase 2 and Phase 3 studies. Injection-site Reactions: In the placebo-controlled studies, injection-site reactions (eg, injection-site rash, erythema) were reported in 0.5% of Trulicity-treated patients and in 0.0% of placebo-treated patients. PR Interval Prolongation and Adverse Reactions of First Degree Atrioventricular (AV) Block: A mean increase from baseline in PR interval of 2-3 milliseconds was observed in Trulicity-treated patients in contrast to a mean decrease of 0.9 millisecond in placebo-treated patients. The adverse reaction of first degree AV block occurred more frequently in patients treated with Trulicity than placebo (0.9%, 1.7% and 2.3% for placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively). On electrocardiograms, a PR interval increase to at least 220 milliseconds was observed in 0.7%, 2.5% and 3.2% of patients treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Amylase and Lipase Increase: Patients exposed to Trulicity had mean increases from baseline in lipase and/or pancreatic amylase of 14% to 20%, while placebo-treated patients had mean increases of up to 3%.

DRUG INTERACTIONS

Trulicity slows gastric emptying and thus has the potential to reduce the rate of absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with Trulicity. Drug levels of oral medications with a narrow therapeutic index should be adequately monitored when concomitantly administered with Trulicity. In clinical pharmacology studies, Trulicity did not affect the absorption of the tested, orally administered medications to any clinically relevant degree.

USE IN SPECIFIC POPULATIONS

Pregnancy - Pregnancy Category C: There are no adequate and well-controlled studies of Trulicity in pregnant women. The risk of birth defects, loss, or other adverse outcomes is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes to maintain good metabolic control before conception and throughout pregnancy. Trulicity should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In rats and rabbits, dulaglutide administered during the major period of organogenesis produced fetal growth reductions and/or skeletal anomalies and ossification deficits in association with decreased maternal weight and food consumption attributed to the pharmacology of dulaglutide.

Nursing Mothers: It is not known whether Trulicity is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for clinical adverse reactions from Trulicity in nursing infants, a decision should be made whether to discontinue nursing or to discontinue Trulicity, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of Trulicity have not been established in pediatric patients. Trulicity is not recommended for use in pediatric patients younger than 18 years.

Geriatric Use: In the pool of placebo- and active-controlled trials, 620 (18.6%) Trulicity-treated patients were 65 years of age and over and 65 Trulicity-treated patients (1.9%) were 75 years of age and over. No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment: There is limited clinical experience in patients with mild, moderate, or severe hepatic impairment. Therefore, Trulicity should be used with caution in these patient populations. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no clinically relevant change in dulaglutide pharmacokinetics (PK) was observed.

Renal Impairment: In the four Phase 2 and five Phase 3 randomized clinical studies, at baseline, 50 (1.2%) Trulicity-treated patients had mild renal impairment (eGFR ≥60 but <90 mL/min/1.73 m^2), 171 (4.3%) Trulicity-treated patients had moderate renal impairment (eGFR ≥30 but <60 mL/min/1.73 m^2) and no Trulicity-treated patients had severe renal impairment (eGFR <30 mL/min/1.73 m^2). No overall differences in safety or effectiveness were observed relative to patients with normal renal function, though conclusions are limited due to small numbers. In a clinical pharmacology study in subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in dulaglutide PK was observed. There is limited clinical experience in patients with severe renal impairment or ESRD. Trulicity should be used with caution, and if these patients experience adverse gastrointestinal side effects, renal function should be closely monitored.

Gastroparesis: Dulaglutide slows gastric emptying. Trulicity has not been studied in patients with pre-existing gastroparesis.

OVERDOSAGE

Overdoses have been reported in clinical studies. Effects associated with these overdoses were primarily mild or moderate gastrointestinal events (eg, nausea, vomiting) and non-severe hypoglycemia. In the event of overdose, appropriate supportive care (including frequent plasma glucose monitoring) should be initiated according to the patient's clinical signs and symptoms.

PATIENT COUNSELING INFORMATION See FDA-approved Medication Guide

- Inform patients that Trulicity causes benign and malignant thyroid C-cell tumors in rats and that the human relevance of this finding is unknown. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, persistent hoarseness, dysphagia, or dyspnea) to their physician.
- Inform patients that persistent severe abdominal pain, that may radiate to the back and which may (or may not) be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue Trulicity promptly, and to contact their physician, if persistent severe abdominal pain occurs.
- The risk of hypoglycemia may be increased when Trulicity is used in combination with a medicine that can cause hypoglycemia, such as a sulfonylurea or insulin. Review and reinforce instructions for hypoglycemia management when initiating Trulicity therapy, particularly when concomitantly administered with a sulfonylurea or insulin.
- Patients treated with Trulicity should be advised of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients treated with Trulicity of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs.
- Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of GLP-1 receptor agonists. If symptoms of hypersensitivity reactions occur, patients must stop taking Trulicity and seek medical advice promptly.
- Advise patients to inform their healthcare provider if they are pregnant or intend to become pregnant.
- Prior to initiation of Trulicity, train patients on proper injection technique to ensure a full dose is delivered. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations.
- Inform patients of the potential risks and benefits of Trulicity and of alternative modes of therapy. Inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and advise patients to seek medical advice promptly.
- Each weekly dose of Trulicity can be administered at any time of day, with or without food. The day of once weekly administration can be changed if necessary, as long as the last dose was administered 3 or more days before. If a dose is missed and there are at least 3 days (72 hours) until the next scheduled dose, it should be administered as soon as possible. Thereafter, patients can resume their usual once weekly dosing schedule. If a dose is missed and the next regularly scheduled dose is due in 1 or 2 days, the patient should not administer the missed dose and instead resume Trulicity with the next regularly scheduled dose.
- Advise patients treated with Trulicity of the potential risk of gastrointestinal side effects.
- Instruct patients to read the Medication Guide and the Instructions for Use before starting Trulicity therapy and review them each time the prescription is refilled.
- Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.
- Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels towards the normal range. HbA1c is especially useful for evaluating long-term glycemic control.

Lilly

Eli Lilly and Company, Indianapolis, IN 46285, USA

US License Number 1891

Additional information can be found at www.trulicity.com

DG HCP BS 18SEP2014

Trulicity™ (dulaglutide) HCP BS 18SEP2014

School Lunch Changes for 2015 May Be Just the Start of Rollback

Mary K. Caffrey

When Congress adopted the Omnibus Appropriations Bill in late December 2014, it featured 2 changes to the National School Lunch Program (NSLP), which came after months of brinksmanship between the School Nutrition Association (SNA) and First Lady Michelle Obama. The changes are not close to a rollback of the 2010 Healthy, Hunger-Free Kids Act, which brought widespread change to what schoolchildren eat for lunch. However, with Republicans having taken control of the Senate and added members to the House this month, more changes may be on the way.[1,2]

The 2010 law took aim at the amount of salt in meals; mandated that half of all grains served in items like pizza, pasta, and biscuits be whole-grain rich; and demanded that more of the calories in school lunches come from fruits and vegetables. The political fracas this fall ignored that these changes stemmed from science: in a November editorial in the *New England Journal of Medicine (NEJM)*, Jennifer A. Woo Baidal, MD, MPH, and Elsie M. Taveras, MD, MPH, noted a 2008 Institute of Medicine report that found school lunches included few fruits and vegetables—except potatoes—and were loaded with refined grains.[3,4]

"Almost 80% of children consumed more saturated fat than was recommended, and sodium intake was excessive in all groups," Baidal and Taveras wrote. "Children ate more than 500 excess calories from solid fats and added sugars per day." With the school lunch program reaching 92% of children and sometimes accounting for the only meals poor children ate all day, change had been imperative to combat rising rates of childhood obesity and diabetes.[3]

For nutrition advocates, frustration stems from the food industry's ability to seize on teenage taste buds and social media to interfere with several nutrition programs—not just school lunches—that were showing early evidence of progress. For example, a February 2014 study in the *Journal of the American Medical Association* found that while one-third of adults and 17% of children were obese, its prevalence had begun to stabilize and obesity rates for the youngest Americans, those 2 to 5 years of age, were falling.[5] Meanwhile, *USA Today* reported that the hashtag #thanksmichelleobama, often accompanied by a photo of an unappealing

In 2008, "Almost 80% of children consumed more saturated fat than was recommended, and sodium intake was excessive in all groups. Children ate more than 500 excess calories from solid fats and added sugars per day."

—JENNIFER A. WOO BAIDAL, MD, MPH, AND ELSIE M. TAVERAS, MD, MPH, WRITING IN THE *NEW ENGLAND JOURNAL OF MEDICINE*

lunch, dates back to 2012. However, it's use began to soar after the midterm elections and peaked November 21, 2014,[6] as the budget deal was taking shape.

IMPLEMENTATION OFFERS SURPRISES, COSTS

The effects of the 2010 law were not felt until the start of the 2012-2013 school year: last-minute rules issued by the US Department of Agriculture (USDA) made implementation difficult and expensive for the same school groups that had supported the law's passage.[7] Almost as soon as school year began, the SNA and the National School Boards Association began complaining that students were refusing to eat cafeteria fare, resulting in financial losses for some school lunch programs and thrown out food, also known as "plate waste."[1,2,7] The math of the school lunch program made losses more likely in wealthy, suburban districts, because fewer children qualify for a free or reduced-price lunch, making the cost of compliance comparatively higher—and the consequences worse when more students opted to bring lunch from home.[8] Of course, more of these schools were located in Republican House districts.

The battle over what school children eat for lunch got ugly enough to be chronicled in a *New York Times Magazine* cover story, which detailed how the fight caused the SNA, a group that represents 55,000 cafeteria professionals, to fire its longtime lobbyist when members fully grasped how the law had changed daily operations. In particular, school cafeteria officials objected to the USDA rule that required students to put fruit or vegetable servings on their tray; otherwise, districts could not be reimbursed for that meal. As the *Times* story outlined, the reality of compelling lunch ladies to demand that burly football players "take your vegetables" just wasn't working on America's cafeteria lines, and some schools were bleeding cash. Meanwhile, kids complained that the meals left them feeling hungry.[7]

By the spring of 2014, the SNA was pressing for a provision that would allow districts operating a net loss to temporarily opt out of the nutrition standards. Michelle Obama and her allies in the nutrition advocacy community fought back, and the compromise in the 2015 budget bill reflects that effort. The budget package takes 2 steps:

- It gives districts more time to achieve increasingly strict standards on sodium content that were scheduled to take effect in 2017. Specifically, budget language locks in the previous sodium reductions in "meals, foods, and snacks sold in schools...until the latest scientific research establishes the reduction is beneficial for children."
- School food directors gained flexibility on the whole grain requirements, which will give them more options for popular food items, like pizza, that make cafeterias money.[1,2,9]

"SNA greatly appreciates Congress' recognition of the challenges school nutrition professionals have faced as they work to meet new nutrition standards," SNA CEO Patricia Montague, CAE, said in a statement. "Since the new standards took effect, 1.5 million dissatisfied students have given up on school meals, taking their lunch money with them."[10]

Nutrition advocates sounded pleased the changes did not go further. "We're pleased that Congress didn't waive all school lunch standards," said Margo Wootan of the Center for Science in the Public Interest. "It's best for kids if school nutrition is based on science, not politics."[1]

TOO MUCH TOO SOON?

Some critics of the sweeping changes have asked whether the real problem was the new standards or the fact that American palates have become so accustomed to salty, fatty fare that it was impractical to make such drastic changes overnight. Schools that had the best success in getting students to accept food meeting the new standards began phasing in the requirements during the 2011-2012 school year, so the new lunches were not such a shock. One superintendent told *TIME* that he agreed with the nutrition standards, but schools couldn't be left alone to force students to eat fruits and vegetables while nothing is done about unhealthy options at McDonald's or gas stations.[8]

In their essay for *NEJM*, Baidal and Taveras cited research that found the longer children are exposed to newer foods, the more likely they are to develop a taste for them; abandoning the

TABLE. A Drop in National School Lunch Program Participation

MONTH	TOTAL PARTICIPANTS
OCT-11	32,251,129
NOV-11	32,268,362
DEC-11	31,727,882
JAN-12	31,821,008
FEB-12	32,087,342
MAR-12	31,655,464
APR-12	31,627,460
MAY-12	30,398,575
OCT-12	31,354,534
NOV-12	31,242,922
DEC-12	30,518,756
JAN-13	30,673,601
FEB-13	30,877,136
MAR-13	30,408,104
APR-13	30,794,341
MAY-13	29,592,315
OCT-13	31,011,250
NOV-13	30,622,677
DEC-13	30,055,744
JAN-14	30,055,744
FEB-14	30,621,613
MAR-14	30,102,901
APR-14	30,408,192
MAY-14	29,243,412
OCT-14	30,921,780

SOURCE: US Department of Agriculture.

FIGURE. Two Lunches, Same Program

At top, an unappetizing lunch shared on Twitter during November 2014. At bottom, a more appealing lunch served during that same period by a school district in West Windsor, N.J. Both comply with the National School Lunch Program.
SOURCE: Top photo, *Washington Post*. Bottom: Photo courtesy of West Windsor-Plainsboro School District.

program only 2 years in, they argue, is not the way to convince American children to eat fruits and vegetables for the long haul.[3] More critically, they cited research that found low-income children—who may not have other food options at home—were more likely to consume the fruits and vegetables served at school.[3,11] Based on these results, will slowing down the phase-in of standards work? More importantly, will the standards survive the new Congress, or the next president?

WHAT HAPPENS NEXT

While the battle over the NSLP has spilled into the public arena, a much quieter process is taking place that could direct how US tax dollars are spent on food programs. On December 15, 2014, the Dietary Guidelines Advisory Committee (DGAC) completed the last of 7 public hearings, and will soon issue its report to the secretaries of HHS and USDA. Recommendations in this report, which will be made public, will inform the 2015 Dietary Guidelines for Americans, which are official US nutrition policy. The guidelines direct the content of the Supplemental Nutrition Assistance Program, meals served to the military, and other programs. The 2010 guidelines informed the law that created the current NSLP.[12,13]

As reported in previous issues of *Evidence-Based Diabetes Management*, current members of DGAC have taken a dietary-patterns approach to their work and have examined the scientific evidence linking what Americans eat to the prevention of common cancers, diabetes, obesity, and heart disease.[12,13] While it's too soon to say what the 2015 guidelines will conclude, any attempt to further ease standards for the NSLP could be in conflict, if the DGAC hearings offer any sign. At its final meeting, for example, the panel called for reducing added sugar in US diets.[14]

"Soda and other sugar-sweetened beverages are unlike most things in the diet in that they provide nothing of value, but are major drivers of diabetes, heart disease, obesity, and other health problems," Michael Jacobson, the director of the Center for Science in the Public Interest, said in a statement praising the DGAC's call for less sugar.[14]

That's not to say that Congress won't have the last word. The 2010 guidelines led to healthier nutrition standards in the Women, Infants' and Children program, and it has been a point of pride with members of the current committee that the last DGAC led to the vouchers that allow WIC clients to purchase fresh fruits and vegetables, but not potatoes. Following lobbying by the potato industry, however, the 2014 Omnibus Appropriations Bill requires HHS to add potatoes to the voucher program.[1]

EBDM

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Results Project Savings for Payers With Novel Oral Anticoagulants

Mary K. Caffrey

Payers in the United States would see a reduction in overall medical costs if patients switched to newer, novel oral anticoagulants, based on a study of 10 clinical trials involving dabigatran, rivaroxaban, and apixaban.

Results of the study were presented December 6, 2014, at a poster session on Health Services and Outcomes Research during the 56th Annual Meeting of the American Society of Hematology (ASH), which took place at the Moscone Center in San Francisco, California.

The study's lead author, Alpesh N. Amin, MD, MBA, consults for Bristol-Myers Squibb (BMS) and for Pfizer, joint makers of apixaban. The authors sought to review recent clinical trials for new oral anticoagulants and compare event rates for patients taking these newer therapies for nonvalvular atrial fibrillation (NVAF) and venous thromboembolism (VTE) with those taking standard therapy or placebo.

In this study, the authors started with treatment costs at the 2013 level and adjusted for inflation, with costs projected from 2014 through 2018. Projections were based on a hypothetical health plan of 1 million members, and prevalence of both conditions was derived from published literature. The authors assumed the same usage rate for all 3 newer therapies when making comparisons.

For 2014, a hypothetical health plan of 1 million insured lives would see medical savings of $3 million by using dabigatran, $2.1 million by using rivaroxaban, and $7.3 million by using apixaban for its NVAF patients.

For acute VTE, savings were $700,000 for dabigatran, $2.2 million for rivaroxaban, and $4.1 million for apixaban. Savings for the VTE patients for extended periods would be $6.3 million for dabigatran, $6.6 million for rivaroxaban, and for apixaban, $9.5 million for the 2.5-mg arm and $9.6 million for the 5-mg arm.

In 2014, savings for the combined NVAF and VTE populations are projected to be $10 million with dabigatran, $10.9 million with rivaroxaban, and $21 million with apixaban. Savings from 2015 through 2018 were projected to steadily rise for all 3 therapies, although the greatest savings relative to standard care would come in the earliest years of treatment. The authors recommend confirming the results in real-world settings.[1]

STUDIES ON SICKLE CELL DISEASE. Two presentations at the December 6, 2014, poster session concerned sickle cell disease (SCD), which received considerable attention at ASH. The first examined patient and caregiver perspectives on adherence to iron chelation therapy (ICT), which is used to manage iron overload in patients with SCD and other anemias who have repeat transfusions. Interviews with 11 patients and 10 caregivers from 6 cities in the United States were coded through a consensus process. Children were not interviewed if they were younger than 9 years.

Respondents said reasons for adherence included perceived positive effects of ICT on health and longevity, support from caregivers and clinicians, and an established routine for taking treatment. Reasons for nonadherence included not liking the taste, aftertaste, or texture of the therapy, or its side effects, such as gastrointestinal symptoms. Mealtime restrictions were also an issue. Caregivers said children who had a greater understanding of the benefits of treatment had better adherence, and that adherence improved as children got older. Several coping mechanisms were reported, such as efforts to mask the taste. The lead author and all but 1 coauthor are employed by Novartis.[2]

A study based at the University of Wisconsin examined the impact of blood transfusion therapy on the quality of life on children with SCD. A group of 196 children in the Multicenter Silent Infarct Transfusion Trial were divided into 2 groups: those who received at least 18 months or more of transfusion (effectively transfused) and those who received less than 18 months. Parents or guardians completed assessments using the Child Health Questionnaire at baseline, at study exit, or at a neurological event. The group was 43% female with a mean age of 9.55 years, and 92% were African American. The groups were equal by gender, disease severity, and rates of pain. At study exit, results showed that children in the effectively transfused group had higher scores in the following areas:

- physical function (M = 12.68, SE = 3.52), t (174) = 3.61, $P \leq .001$;
- bodily pain (M = 13.16, SE = 3.74), t (174) = 3.51, $P \leq .001$;
- change in health (M = 0.39, SE = 0.14), t (166) = 2.71, P =.01.[3]

The authors described these results as the first evidence that blood transfusion improves health-related quality of life for children with SCD. Mast Therapeutics provided research funding for the study. **EBDM**

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Study Suggests Method of Reducing Blood Clots Without Risking Bleeding

Mary K. Caffrey

It's long been assumed that clinicians who treat patients to avoid blood clots must risk consequences: the potential for bleeding. A study named one of the "Best of ASH" at the 56th Annual Meeting of the American Society of Hematology, and simultaneously published in the *New England Journal of Medicine*, works around that problem, and it could give clinicians a safer way to limit blood clots, with enormous safety potential for patients.[1]

Factor XI, an important enzyme in the coagulation pathway, is naturally reduced in some people, and this group is at a lower risk of venous thromboembolism (VTE). So, the reasoning went, if Factor XI was reduced by other means in patients undergoing a surgical knee replacement—a procedure with high risk for blood clots—would the patients have reduced VTE?

First presented at a press conference December 7, 2014, and then at the late-breaking abstract session December 9, 2014, the study led by Harry Büller, MD, PhD, of the Academic Medical Center of the University of Amsterdam, the Netherlands, described how researchers used injectable nucleic acid engineered to reduce Factor XI expression.

At the press conference, Büller could barely contain his excitement about the results and confessed he had grown weary of holding in his secret. "This is the holy grail," he said. The ability to decouple treatment for blood clots from bleeding episodes could revolutionize surgical care and reduce medical costs. His study was 1 of 4 related to blood clots discussed at the news conference, while efforts to control bleeding and hold down its related costs gained notice at ASH in 2014.[2]

In a randomized controlled trial, approximately 300 patients having total knee replacement received an interfering agent for Factor XI, in doses of either 200 or 300 mg, or the anticoagulant enoxaparin at 40 mg. Patients received subcutaneous injections of Factor XI starting 36 days before surgery to allow time for the treatment to interfere with Factor XI production, with the last dose 3 days after surgery. Those in the control group received enoxaparin for 8 days after surgery.

Subsequently, patients receiving 300 mg of a Factor XI interfering agent had the lowest occurrence of VTE (4.2%, 3 of 71 patients), compared with those receiving 200 mg of the Factor XI agent (26.9%, 36 of 134 patients) or enoxaparin (30.4%, 21 of 69 patients). Also, those who received the Factor XI interfering agent had fewer bleeding incidents than those who had enoxaparin (bleeding rate of 2.6% in the high-dose Factor XI agent

group compared with 2.8% in the low-dose group and 8.3% for the anti-coagulant group.) Researchers found the Factor XI interfering agent did not increase bleeding and did not interfere with other aspects of coagulation.

BLOOD CLOTS AND CANCER. A pair of studies involving blood clots and cancer were presented at the December 7, 2014, press conference. Data gathered by researchers from the Netherlands examined 926 cancer patients from 11 studies or registries who had lung scans for other reasons that recorded incidental pulmonary embolism (IPE). Researchers found that the chance of developing a second clot was nearly double in cancer patients with IPE who did not receive continued anticoagulant treatment, compared with those who had low-molecular weight (LMWH) heparins or vitamin K antagonists or VKAs (12% compared with 6.2% or 6.4%). Six-month mortality was higher in untreated patients (47%) than in patients with LMWH or VKAs.[3]

Another study found that tinzaparin, a LMWH, was more effective than warfarin for treating actue VTE in cancer patients. The results discussed by Agnes Lee, MD, of the University of British Columbia in Vancouver, Canada, were also presented at the late-breaking session. They essentially confirm a single trial on which current guidelines are based. Lee explained that study participants received either tinzaparin once daily for 6 months or tinzaparin once daily for 5 to 10 days, followed by 6 months of warfarin. During the treatment period, 31 patients (6.9%) treated with tinzaparin experienced recurrent VTE compared with 45 (10%) patients treated with warfarin. Tinzaparin was only statistically significant in reducing recurrent VTE in veins above the knee. Researchers did not observe a difference in the mortality or incidence of major bleeding events (2.9% in the tinzaparin arm and 2.7% in the warfarin arm), but noted that significantly fewer patients experienced clinically relevant, non-major bleeding with tinzaparin than warfarin (11% vs 16%). Under questioning, Lee acknowledged that warfarin is significantly less expensive than tinzaparin and other LMWH and heparins, and press conference moderator Mary Cushman, MD, of the University of Vermont in Burlington, said that her hospital defaults to warfarin if patients cannot get insurance coverage for heparins.[4]

NOACS IN REAL-WORLD SETTINGS. Newer medications than warfarin, known as novel anticoagulants (NOACs), do cost more but require less monitoring to assess bleeding risk, and there is no recommended standardized dose. Three newer anticoagulants—dabigatran, apixaban, and rivaroxaban—may help patients avoid these other nonmedication costs. A study presented December 7, 2014, examined bleeding risks outside of a clinical trial setting. Martin H. Ellis, MD, of Meir Medical Center in Kfar Saba, Israel, presented a population analysis that looked at 18,249 patients with atrial fibrillation who took warfarin or a NOAC (dabigatran or rivaroxaban) between January 1, 2011, and December 31, 2013. Patients taking warfarin had 3.9 bleeding episodes per 100 patient years, while those taking dabigatran had 2.8 (150 mg twice daily) or 4.6 (110 mg twice daily), and 4.3 episodes on rivaroxaban. Ellis said the slightly higher bleeding rate on the lower dose was explained by doctors managing the doses of patients who started out with higher risks of bleeding. He noted that while the newer therapies present advantages, there are still risks, and patients and physicians must be alert.[5] **EBDM**

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Recommendation on Anticoagulants Part of Latest Round of ASH *Choosing Wisely* Initiative

Mary K. Caffrey

A call for limiting how long to use anticoagulants after an initial venous thromboembolism was included on the second list of tests and treatments to question as the American Society of Hematology (ASH) issued a fresh set of recommendations under the Choosing Wisely initiative.[1] This year's list was announced at the start of the 2014 ASH Annual Meeting that convened at the Moscone Center in San Francisco, California. The first round of recommendations, numbers 1 through 5, were announced December 4, 2013, at the last ASH meeting in New Orleans, Louisiana. Details of recommendations 6 through 10 were presented at a session December 8, 2014.


Mark Crowther, MD, MSc

Mark Crowther, MD, MSc, of McMaster University in Hamilton, Ontario, Canada, discussed the recommendation, "Don't use anticoagulants for more than 3 months in patients with a first venous thromboembolism (VTE) occurring in the setting of a major transient risk factor."

Crowther described this recommendation as a basic calculation of benefit-versus-risk: a VTE triggered by a major event, such as surgery, presents a low risk for recurrence once the major event has passed and recovery has occurred, assuming adequate care and anticoagulant therapy. Subsequently, such patients have a low risk of thrombosis, "and have the same risk of bleeding as other patients." The ASH recommendation does not apply to VTE linked to nonmajor risks, such as pregnancy or travel-associated immobility.

Choosing Wisely is the initiative of the American Board of Internal Medicine Foundation that asks each specialty to identify tests or treatments that might be overused and unnecessary, with the potential to harm patients. While saving healthcare dollars is not the only consideration of Choosing Wisely, its efforts will have that effect if patients and their doctors are more judicious in their medical decisions.

While cost savings is not the only consideration of Choosing Wisely, *it will have that effect if patients and their doctors are more judicious in their decisions.*

Other ASH Choosing Wisely recommendations are:

- **Don't perform baseline or routine surveillance computed tomography scans in patients with asymptomatic, early-stage chronic lymphocytic leukemia.** This recommendation incorporates a theme heard this year at ASH about overuse of scans, which has been a broad theme across managed care and cancer care especially.
- **Don't test or treat for suspected heparin-induced thrombocytopenia in patients with a low pre-test probability.** Adam C. Cuker, MD, MS, of the University of Pennsylvania, described the "4T" score, a widely used system that allows clinicians to evaluate the timing of a degree of thrombocytopenia and whether it might be caused by heparin. Cuker said this is one of the tough calls in medicine: for one, a patient is taken off heparin and other anticoagulants are much more expensive.
- **Don't treat patients with immune thrombocytopenic purpura in the absence of bleeding or low platelet count.** Cindy R. Neunert, MD, of Georgia Regents University, noted that this ASH recommendation applies to adults and that pediatric cases have difficult criteria. Treatment should be aimed at improving quality of life without exposing patients to unnecessary risks and is always conditioned on prior bleeding episodes, activity levels, and social factors. **EBDM**

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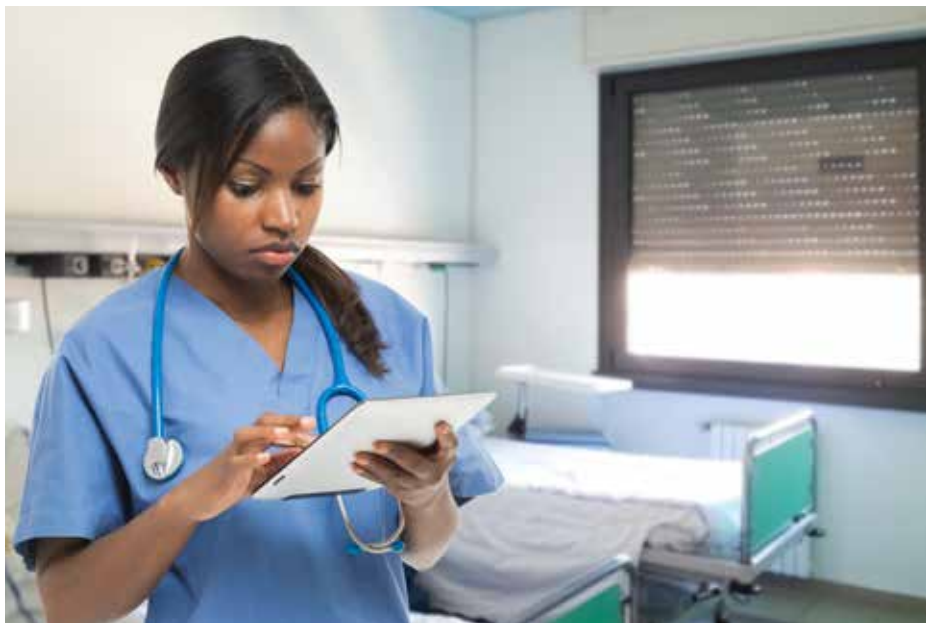
Race and Gender, Additional Risk Factors in Diabetes for Night-Shift Workers, Study Finds

Surabhi Dangi-Garimella, PhD

A huge prospective cohort study, currently ongoing in academic centers in Massachusetts, has identified that African American women who had extended periods of night-shift work had an increased incidence of type 2 diabetes mellitus (T2DM).[1] The Black Women's Health Study (BWHS) followed 28,041 women from 2005-2013, based on a questionnaire that identified them to have worked the night shift.

Previous research has shown that shift work reduces employee wellbeing; working nights—or worse, rotating shifts—increases the risk of obesity, insomnia, hypertension, stomach ulcers, depression, workplace injury, tobacco use, heart disease, and diabetes.[2] Another recent meta-study, published in *Occupational & Environmental Medicine,* found that any amount of time spent doing shift work increases the risk of diabetes by 9%.[3] Interestingly, the results, the product of a meta-analysis of 12 international studies, found a more significant correlation between shift work and diabetes in men than in women.



Some professions, like nursing, demand that some staff members work the night shift. A new study finds that working nights may put African American women at risk for developing diabetes.

The Black Women's Health Study (BWHS) followed 28,041 women from 2005-2013, based on a questionnaire that identified them to have worked the night shift. The study found that African American women who had extended periods of night-shift work had an increased incidence of T2DM.

The BWHS study found that during the 8 years of follow-up, 1786 women developed diabetes. Relative to women who had never worked the night shift, hazard ratios (HRs) (95% CI) for diabetes were 1.17 (1.04, 1.31) for 1 to 2 years of night-shift work, 1.23 (1.06, 1.41) for 3 to 9 years, and 1.42 (1.19, 1.70) for ≥10 years ($P < .0001$). The study results found a 23% increased incidence of T2DM among women who had the longest duration of working the night shift. Further, while obesity did not seem to influence disease prevalence, women older than 50 years working the night shift had a lower incidence of diabetes.

The authors conclude that their study has broad societal implications, considering that a high percentage of employees in the United States work the night shift, and they suggest that circadian adaptation for shift-work employees needs more attention and research. **EBDM**

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Results from Scotland Show Persons With Diabetes Living Longer, Especially Those With T1DM

Adam Hochron

Researchers in Scotland have shown that although diabetes is a growing problem for that country's population, patients diagnosed with the condition are living considerably longer than they have in the past. This is particularly true for patients diagnosed with type 1 diabetes mellitus (T1DM).

The results were recently published in the *Journal of the American Medical Association*.[1] Using data on patients with diabetes in the country who were at least 20 years old between 2008 and 2010, the team had a patient pool of 691 individuals representing 67,712 person-years also reported 1043 deaths during that time.

The results of the study showed that males who lived until at least the age of 20 were expected to live another 46 years if they had T1DM, and 57 more years if not for an estimated loss in life expectancy of just over 11 years (95% CI, 10.2-12.1). For females who lived until at least the age of 20, diabetes patients were expected to live another 48 years with the condition or an additional 61 years without it for a slightly higher loss of life expectancy of 12.9 years.

Study results also showed that patients with an estimated glomerular filtration rate of 90/mL/min/1.73m^{2}or higher saw their life expectancy reduced 49 years for men and 53.1 years for women. This resulted in an estimated loss lo life expectancy of 8.3 years (95% CI, 6.5-10.1) for men and 7.9 years (95% CI, 5.5-10.3) for women.

"Overall, the largest percentage of the estimated loss in life expectancy was related to ischemic heart disease (36% in men, 31% in women) but death from diabetic coma or ketoacidosis was associated with the largest percentage of the estimated loss occurring before age 50 years (29.4% in men, 21.7% in women,) the authors noted.

Looking at the averages for people with as opposed to those T1DM, without the condition, the authors reported an average loss of life expectancy of 11 years for men, compared with their healthier counterparts, and 13 years for women, compared with the overall population of the European country. **EBDM**

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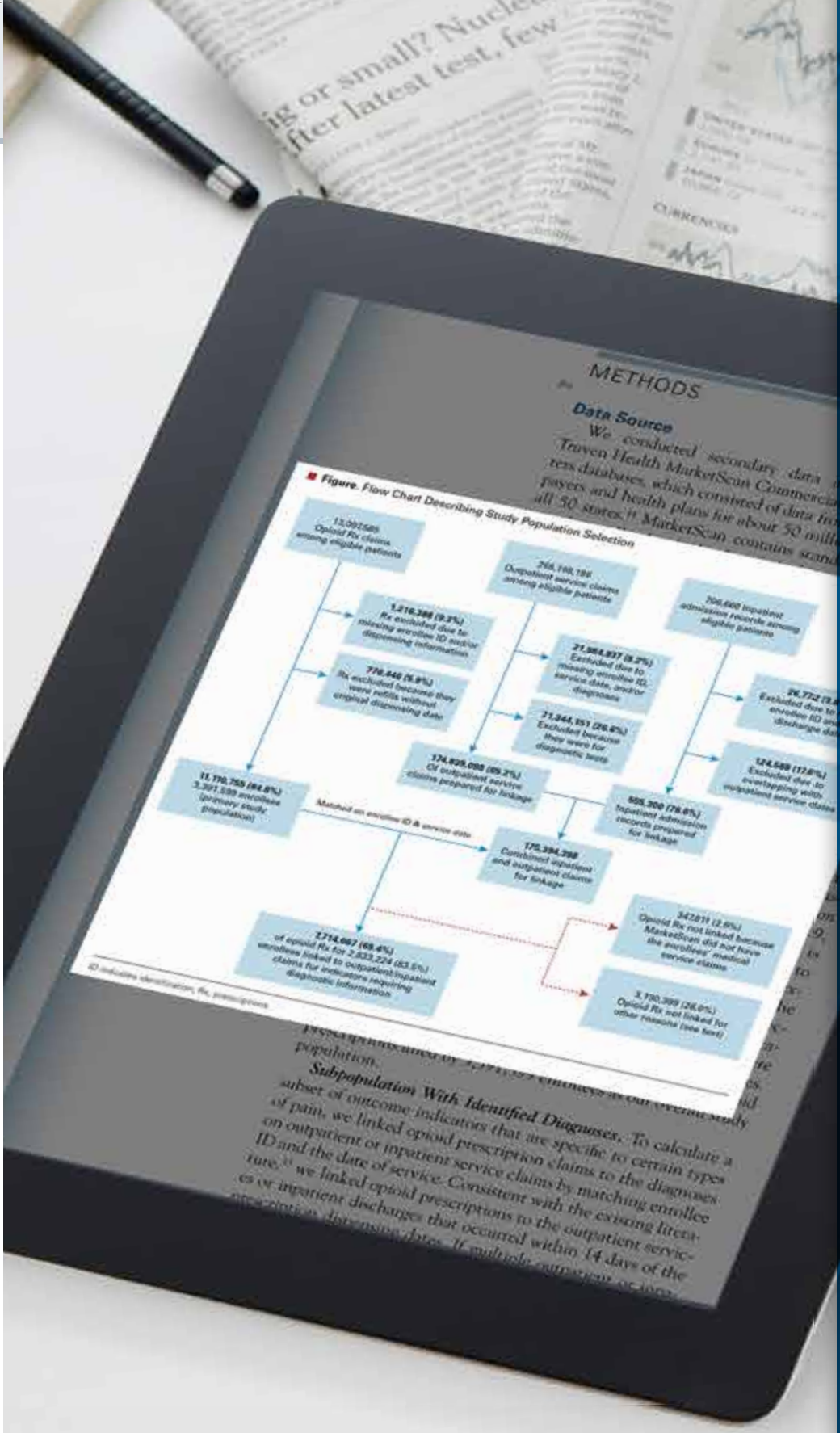

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Optimal Health Requires More Than Medication
(CONTINUED FROM COVER)

Ed Pezalla, MD, vice president, national medical director for Aetna Pharmacy Policy and Strategy; Mark Friedlander, MD, chief medical officer for Aetna Behavioral Health; and Mary Von, RN, senior project manager, Aetna Behavioral Health

Most medication nonadherence stems from patients choosing not to take their medications based on beliefs about their treatment, diagnosis, and prognosis. They may choose not to fill their prescriptions, take the medication infrequently, or stop taking medication altogether due to side effects or other concerns.


Ed Pezalla, MD, MPH

with and without insulin, is an important goal for diabetics and helps to prevent a number of vascular and neurologic complications and related disabilities. Effective adherence to medication regimens will improve both outcomes and quality of life for patients, and reduce both direct and indirect costs.

Reminder programs, timers, electronic pill boxes, and other devices can be great tools for helping patients who are forgetful or are on complex medication schedules. Additionally, plan designs, such as Aetna RX Healthy Outcomes, remove or lower the co-payment for targeted drugs to help address financial barriers. However, even a $0 co-pay does not always result in perfect adherence.

Most medication nonadherence stems from patients choosing not to take their medications based on beliefs about their treatment, diagnosis, and prognosis. They may choose not to fill their prescriptions, take the medication infrequently, or stop taking medication altogether due to side effects or other concerns. Studies that examine intentional and unintentional nonadherence show that 80% of medication nonadherence is deliberate. Further, despite much attention, health literacy accounts for only 20% of nonadherence.

ENGAGING MIND AND BODY

Patients are not pill-taking machines, and medication adherence alone is not the answer to improving health. Healthy diet and exercise can also deliver significant health benefits. Still, the disease is only one part of a person's life. Medication, diet, and exercise must be incorporated into a person's existing routine in a way that is both realistic and sustainable—and that requires motivation.

Health plans, both insured and employer-sponsored, often feature incentives and reward programs for healthy actions. These external motivators may include a reduction in premiums for completing an activity, such as answering a health risk–assessment questionnaire or reaching a health goal (target cholesterol levels, healthy weight, steps walked, etc).

Taken a step further, programs like Aetna's Metabolic Syndrome Program assess a person's current risk for metabolic syndrome. This group of 5 closely-related conditions—increased blood pressure, elevated blood sugar, excess body fat around the waist, low HDL, and high triglyceride cholesterol levels—can increase a person's risk of heart disease, stroke, and diabetes. The more conditions a person has at one time, the greater the risk. However, metabolic syndrome can be reversed by making changes to diet, losing weight, and exercising. Aetna's program provides a detailed, personalized health report with suggested steps that help prompt the member to take action to better health. While both incentives and actionable information can provide a great start, continuing the journey to better health requires development beyond external motivators to internal motivation.

DEVELOPING THE INNER DRIVE

Suppose a person takes up jogging to lose weight and increases the amount of aerobic activity that he can log in his employer-sponsored health challenge, he may be rewarded for meeting a new health goal. But, over time, those rewards begin to matter less. To keep running, he needs to want to run. Running—not the external reward—becomes the goal. The satisfaction that he feels when he completes a run, logs miles for the week, or enjoys the camaraderie of being with like-minded individuals at a local 5K race are all rewards in themselves. The popularity of Team-In-Training and the high participation rates in marathons and races of all lengths demonstrate the power of internal motivation.

Recognizing the importance of internal motivation, Aetna's care management programs have integrated motivational interviewing (MI) techniques to help people identify and develop internal motivators. Instead of telling people why they need to follow a treatment or just rewarding them for doing so, nurses and health coaches help each individual develop a unique set of internal motivators. MI focuses on mutual, personal guidance and has been proved in clinical studies to decrease resistance and enhance motivation to change. Building from this evidence, Aetna health coaches can better empower members in their care.

Practicing the principles of motivational interviewing, Aetna's disease management nurses have an enhanced ability to create a safe place for members to focus on their health. Nurses elicit, rather than impose, motivation to change. They help members explore and reinforce their own arguments for change, and then guide fully informed and autonomous choices.

Practicing the principles of MI, Aetna's disease management nurses have an enhanced ability to create a safe place for members to focus on their health. Nurses elicit, rather than impose, motivation to change. They help members explore and reinforce their own arguments for change, and then guide fully informed and autonomous choices. Creating a highly personalized member experience with real conversations, not scripted interactions, encourages members to take greater responsibility for their actions and health.

Studies also demonstrate that adherence improves in patients who report a good relationship with their physician, with effective communication being an important factor in those relationships. A patient-centered approach to care promotes a partnership in making decisions about medication, considers cultural beliefs and attitudes, and actively encourages input and feedback from the patient.

TECH SUPPORT FOR HEALTH

Mobile technology is transforming the world, and health care is no different. Patients have a growing selection of phone apps and Web-based tools to help inform, connect, motivate, and track their health goals. Several adherence apps are free and have companion websites that allow physicians to enter their patients' prescriptions. Many have privacy-compliant cloud data storage that can be accessed from the doctor's office, updated, and delivered to the patients' mobile devices. Customized reminders also can be set up, and information on doses taken or missed can be exported to the doctor's office for review. Still, technology alone has limited benefits. Many of the apps rightly have disclaimers advising that patients should not rely on an app alone to remember to take medications.

Addressing the problem of chronic disease management requires approaching people as an entire being, not as a machine fuelled by pills. Rather than focusing on medication adherence alone, patients need access to a combination of external and internal motivators that can help them start and maintain a routine that successfully integrates medication, healthy diet, and exercise. When health plans, plan sponsors, healthcare providers, and patients can work more closely to ensure all of the elements are considered and supported, better health outcomes will follow. **EBDM**

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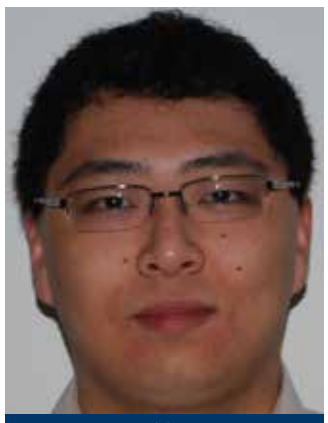
Patient Adherence and CMS Reimbursement Policies for Combination Oral Anti-Diabetic Therapies
(CONTINUED FROM COVER)

patient adherence to prescribed medication regimens. By reducing a patient's pill burden, especially for those with additional comorbidities requiring dual or triple therapy, an FDCT product may offer a more convenient administration option compared with loose-dose combination therapy (LDCT) with individual products.

Several studies have evaluated the impact on adherence rates of switching patients from dual therapy to FDCT. One retrospective cohort analysis of 7570 FDCT users and 14,762 LDCT users in the Texas Medicaid prescription claims database showed a 12.4% increase in patient adherence.[1] A separate study focusing on patients treated with pioglitazone and metformin found an 8.9% increase in adherence when switching from LDCT to FDCT,[2] and analyses of 17 different studies conducted between 1998 and 2009 yielded similar results, with improvements in adherence ranging from 10% to 13% with FDCT compared with LDCT.[3]


David Yao

The increased adherence seen with FDCT products translated into improved clinical outcomes and cost-effectiveness for patients. Several studies analyzing the effect of nonadherence to prescribed oral anti-diabetic regimens on glycemic control found increased risks of all-cause hospitalization and mortality due to complications from poorly treated diabetes.[3] The subsequent economic burden of these complications was also evaluated, and a retrospective analysis of 100,000 patients with T2DM found annual increased healthcare costs of $336 and $1509 for nonadherent metformin and sulfonylurea users, respectively, compared with adherent users.[3] These figures were obtained even after accounting for the increased cost of medication that comes with improved adherence, showing that the medication cost was more than offset by the cost savings from averted hospitalizations.[3] The cost of an FDCT product (Actoplus Met, pioglitazone/metformin) compared with its analogous LDCT products was also studied, and the FDCT product was found to be $0.26 less per tablet compared with the LDCT products, leading to a cost savings of approximately $8 per patient per month with FDCT therapy.[2]

CMS REIMBURSEMENT POLICIES FOR FDCT PRODUCTS

Despite these findings, which support the clinical efficacy and economic benefits of FDCT therapy, a cost-cutting battle continues over the formulary inclusion status of these products in Medicare Prescription Drug Benefit Program (Part D) plans. CMS proposed a change for 2015, struck down in June 2014, that would have made FDCT products exempt from being required on the formularies of Part D plans. The rationale given for this change was that because all individual medications in a given therapeutic class would be included on the formulary as single-entity products, requiring the inclusion of FDCT products would be redundant and unnecessary.

The proposed change would also have both encompassed protected therapeutic classes such as anticonvulsants and antineoplastics, which traditionally include all medications in the class on formulary without restrictive prior authorization requirements,[4] and removed the protected designation for immunosuppressants, antidepressants, and antipsychotics, which would reduce the number of medications on formulary for these classes in a bid to lower drug costs. CMS proposed that antiretroviral medications be excluded from this exception, under the rationale that nonadherence to treatment in this therapeutic class presented far more serious clinical consequences than in other cases. As such, CMS concluded that the benefit of increased adherence with antiretroviral FDCT products would warrant formulary inclusion in addition to the single-entity products.[4] For now, there are no active proposals to exempt FDCT therapies in protected drug classes from required formulary inclusion. However, it remains to be seen what future guidance CMS will issue regarding FDCT medications, as the agency continues to pursue cost-cutting strategies while considering the potential clinical and economic benefits of these products.

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FDA POSITION ON FDCT PRODUCTS

The proposed changes to Medicare Part D regarding FDCT products come even as the FDA has reconsidered exclusivity rules for such therapies. In recognition of the clinical and cost-effective benefits provided by FDCT products, the FDA finalized an industry guidance in October 2014 that extended exclusivity to 5 years for newly approved FDCT products that combine a New Chemical Entity (NCE) with previously approved components. This benefit, however, will not apply retroactively; any FDCT products approved prior to finalization of the guidance will still have the former 3-year period of exclusivity. In making this change, the FDA noted the benefits of FDCT products, such as improved patient adherence and clinical outcomes, as well as advantages in certain therapeutic areas, such as anti-infectives in combating drug resistance. As such, the FDA considered the change in exclusivity rules an incentive to encourage the development of novel FDCT products.[5] **EBDM**

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On the Horizon in Diabetes Therapy: A Delivery System That Doesn't Rely on the Patient
(CONTINUED FROM COVER)

The only way to consolidate a year's worth of medication into an implantable device is to start with an incredibly potent medication, and it would be hard to find one more potent than exenatide. In 2005, the FDA approved the drug for use in T2DM patients at 2 tiny doses: 10 or 20 *micrograms* per day.[5] Those doses equate to 3.65 or 7.3 mg per year. A single tablet of extra-strength acetaminophen, by comparison, contains 500 mg of medication.


Robert R. Henry, MD

Of course, the medicine inside an implantable device must also be stable enough to remain at body temperature for months on end without degrading. Exenatide, in its original formulation, failed miserably on this front. It was a synthetic hormone that degraded almost immediately under anything short of optimal conditions. The notion of using it inside an implantable device only became possible when researchers at Intarcia Therapeutics, a Boston-based company, discovered a technique for stabilizing proteins, peptides, and antibodies at very high temperatures. Intarcia's executives quickly realized that this stabilization process would allow medications to remain potent for long periods inside the human body. The only real obstacle was distribution. However, as they soon discovered, another company had already designed osmotic mini-pumps that could release a steady stream of medication into the body for years on end. Intarcia bought the rights to that technology and, shortly thereafter, began testing its lead product.

The most recent information about ITCA 650's performance came out in October, when Intarcia announced top-line results of 2 phase 3 trials of the formulation.

The first of those trials randomized 460 patients with A1C levels between 7.5% and 10% evenly among placebo and 2 doses of ITCA 650, 40 mcg per day and 60 mcg per day. (Doses of Intarcia's formulation are higher than approved doses of exenatide because earlier trials demonstrated 40 mcg and 60 mcg to be more effective than lower doses of the form of the drug and delivery system.)

Patients in the active arms started with 3-month devices that delivered an initial dose of 20 mcg per day, and then received 6 months of treatment at one of the 2 trial doses. Those who eventually received the lower trial dosage of 40 mcg saw their A1C levels drop an average of 1.4 percentage points, and those who received the higher dosage of 60 mcg saw their A1C levels drop an average of 1.7 percentage points. Both of those reductions significantly bested results for patients in the control arm of the trial.[6]

Intarcia announced these results, of the FREEDOM-1 and FREEDOM-1 high baseline phase 3 trials, in an October press release. The company said it was submitting full findings for presentation at the 75th Annual Meeting of the American Diabetes Association, scheduled for June 2015 in Boston.[6]

The second set of results involved patients with A1C levels between 10% and 12%, and gave them 20 mcg per day for 3 months and 60 mcg per day for an additional 6 months. Patients in this second trial started with average A1C levels of 10.8% and ended, on average, 3.4 percentage points lower at 7.4%. These results, which were considered preliminary, were presented at the 50th meeting of the European Association for the Study of Diabetes in Vienna, Austria, which took place September 15-19, 2014.[7]

Many of the patients in both of the trials were already using 1 or more oral treatments when their trial started. Such patients continued using those medications throughout the trial and, thus, used ITCA 650 as part of a combination therapy. Some patients, however, particularly in the first trial, were not using medications when they enrolled and, thus, used ITCA 650 as monotherapy. The medication provided significant benefits in both cases.

"I think this device has the potential to be a true game changer," said Robert Henry, MD, a professor of medicine at the University of California at San Diego and the director of the Center for Metabolic Research at the VA Medical Center in San Diego. Henry, like Skyler, does consulting work for Intarcia, among other pharmaceutical companies, and he has participated in ITCA 650 trials.

"The medication reduces A1C levels in virtually everyone. Only 2 of 60 patients in a recent trial I led did not experience reductions of at least 0.5%. It also produces significant weight loss—3% of body weight, on average—in most people. And it requires no effort from patients. The pump, to my knowledge, has never failed. It just works."

Intarcia is currently undertaking 2 more phase 3 trials, and if they meet their goals, the company expects to submit ITCA 650 for FDA approval in early 2016. Doctors who have used the treatment in trials are counting the days. "With continued success in the remaining phase 3 trials, we should have a real game-changing therapy available soon to help physicians to better manage this serious disease," Henry said. If ITCA 650 does win FDA approval, it will constitute a significant step on the road toward easier treatments for T2DM.

Patients who had the disease in the early part of the last century had no option other than insulin injections. That changed in 1955 when drug makers introduced the first oral medications that stimulate the pancreas to make more insulin.[8] In the early days, these oral medications were often used in addition to injections, rather than as a replacement, but as oral therapies have improved, more patients have stopped using any kind of injection. Nearly 57% of all Americans with diabetes now solely use oral medications to treat their condition.[2]

Still, many patients fail to follow the treatment plans prescribed by their doctors. According to a recent review of research on patient compliance, more than one-third of all patients eat things they should avoid, and more than 80% of them exercise too little. In fact, electronic monitoring of pill consumption found that adherence rates for oral medication ranged from 53% to 67%.[9] Specialists say that even fewer patients with T2DM religiously follow instructions for using injectable medication. These failures trigger many of the complications that exact such a physical toll on people with diabetes and such a financial toll on the American medical system.

That toll has ballooned in recent years as America has grown older, fatter, and more racially diverse. The number of people diagnosed with T2DM grew from about 6 million in 1980 to more than 21 million in 2011,[10] and the problem will likely get worse. Another 86 million Americans 20 years and older had prediabetes as of 2012, and experts estimate that one-third of all Americans will eventually develop the condition.[11] Unless people with diabetes begin controlling their condition better than they have to date, such an increase in patient numbers will threaten the solvency of the healthcare system and ruin millions of lives.

Countless initiatives are already under way in nearly every corner of the healthcare system to help patients get a better handle on their disease: local governments are making restaurants put calorie counts on menus, employers are subsidizing gym memberships, insurers are adjusting co-pays, doctors are joining accountable care organizations, and drug makers are spending billions on research.

Intarcia joined this widespread fight against diabetes in the mid-2000s, shortly after one of its experimental medications failed in phase 3 trials. The privately held company had focused on cancer medications since it opened its doors in 1997, but its owners were considering all their options, including liquidation, when several Intarcia researchers discovered the technique for stabilizing proteins, peptides, and antibodies at high temperatures.

"Their announcement came as a total surprise. No one else in the company even knew they'd been working on the project, but the importance of their discovery was immediately obvious," said Intarcia CEO Kurt Graves. "These biological compounds are some of the best treatments we have for a wide range of diseases, but they're totally unstable at room temperature, let alone body temperature. That makes them hard to manufacture and hard to store and hard to use, and that, in turn, limits their usage and makes them expensive. Finding a way to keep these medicines stable at body temperature for years on end was like finding the Holy Grail."

Intarcia patented the technique, of course, but Graves still declines to explain it in anything but the broadest terms: Intarcia imbeds unstable medications in a suspension formula that keeps them fixed indefinitely. Company researchers have yet to determine how long its process can keep fragile medications in working order. They have kept some bottled samples at 105 degrees for more than 3 years now, and those samples show no sign of deterioration.

Still, it was quickly apparent that the process worked well enough to create something unprecedented in the treatment of chronic illnesses: once-a-year implants that delivered continuous medication. Intarcia, therefore, began looking for approved medications that were suitable candidates for its stabilization technique and the micro-pump technology that it acquired for product delivery.

Many biological medications appeared insufficiently potent for long-term delivery. A year's supply of a medication with a therapeutic dose of 500 mg per day would require an implant the size of a bread box, which, presumably, would not be very comfortable. Exenatide, however, looked about as promising as a candidate could look: a very effective treatment for a very common disease that was used by relatively few people because its fragile formulation could only be taken by injection.

Despite the existing approval for exenatide, Intarcia put ITCA 650 through a full trial process and submitted a new drug application to the FDA in an attempt to prove that its stabilization process did not increase side effects or, conversely, stabilize the drug so much that it provided no therapeutic value.

Trial results to date indicate that the stabilization process and continuous delivery affect both the medication's efficacy and its side effect profile. Fortunately, they seem to increase the former and decrease the latter. It is unclear whether the increased efficacy stems entirely from eliminating the dosing errors that took place when exenatide was tested as an injection or whether other factors, such as continuous delivery, play a role. As for the reduction in side effects—especially the nausea that is common with exenatide injections—Intarcia's scientists and some of the researchers who have worked on ITCA 650 trials generally credit the transition from concentrated injections to a small but steady stream of medication. Whatever the reason, Intarcia executives believe that the combination of effortless administration and negligible side effects might allow them, eventually, to get expanded approval for ITCA 650, approval that would allow them to use the product both as a treatment for T2DM and as a tool for preventing people with prediabetes from developing the disease.

"We haven't announced pricing yet," Graves said. "But the stability of our formulation of this medication greatly reduces manufacturing and handling costs, so we could price ITCA 650 far closer to an oral therapy than a typical biologic injection….At that sort of price, it could certainly make sense to use it for prevention as well as treatment." **EBDM**

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