Bridging the gap between payer and provider perspectives

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Evidence-Based Diabetes Management™

In the Workplace

New Research Shows Employers Need Strategies to Help Night Shift Workers Avoid Diabetes

Andrew Smith

New research into the link between shift work and type 2 diabetes mellitus (T2DM) further quantifies a well-established but underappreciated fact: irregular hours significantly reduce employee well-being and raise healthcare costs.

While some employers have begun taking steps to mitigate the damage, reports on companies eliminating nonessential shift work have been scarce, and most employers have yet to address the issue despite its enormous impact on the 16 million Americans who regularly work at odd times.[1]

A growing body of research shows that working nights—or worse, rotating shifts—increases the risk of obesity, insomnia, hypertension, stomach ulcers, depression, workplace injury, tobacco use, heart disease, and, diabetes.

"The health risks are big enough that all people should consider them before taking on shift work," said Frank Hu, MD, PhD, a professor of nutrition and epidemiology at the Harvard School of Public Health, in an interview with *Evidence-Based Diabetes Management*.

"People who are in poor health or at risk of developing a related disease, especially diabetes, should probably avoid shift work if they can. Those people who do take it should pay extra attention to diet, exercise, and sleep. They should also get screened regularly for signs of diabetes and other health problems."

> *"People who are in poor health or at risk of developing a related disease, especially diabetes, should probably avoid shift work if they can. Those people who do take it should pay extra attention to diet, exercise, and sleep."*
>
> **—Frank Hu, MD, PhD**

Hu coauthored a paper that analyzed the ties between shift work and diabetes in 177,000 nurses who participated in a pair of long-term general health studies. Published in *PLoS Medicine*, the paper reported that women who worked rotating night shifts for 1 year or 2 years were 5% more likely to develop diabetes over the following 20 years than women who only worked days.[1]

Women who spent more time working rotating night

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Personal Technology

Technology in Diabetes Apps Improves, But Will It Bring a Change in Behavior?

Andrew Smith

The announcements flow steadily from computing giants, from software startups, and from medical specialists such as Dexcom, which now sells a device that automatically sends glucose readings to tablets and smartphones.[1] Each day brings some new wireless technology or smartphone software that helps patient with diabetes monitor and manage their health. Many of these improvements automate the process of data collection. Others present data in useful ways. Still others transform it directly into advice for immediate action.

All that news has generated much excitement about a general revolution in personal healthcare,[2,3] but questions remain about the true impact on day-to-day well-being. Optimists expect major improvements in the not-too-distant future. Technology, they believe, will soon automate not only the laborious task of collecting data on nutrition, exercise, and blood sugar, but also the complex process of using those data to calculate optimal behavior.[2] Patients who now complain of working a second job to care for chronic ailments will live easier, healthier lives.

Pessimists disagree. They predict significant limitations in technology's ability to collect some of the most meaningful data and to make treatment decisions that take into consideration how dramatically patient responses can vary in seemingly identical situations.[3] Pessimists also dispute the underlying notion that people today suffer poor health because of a lack of information rather than an inability to force themselves to

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Commentary

Team-Based Approach to Care Management

Patrick Gilligan

Senior Vice President, Health System Alliances, CVS Health

Chronic diseases are among the most prevalent and expensive of all health-related conditions. Nationwide, 75% of healthcare spending is attributable to the treatment of chronic diseases.[1] In recent years, diabetes has gained prominence as one of the most concerning chronic diseases by virtue of increasing disease prevalence and cost burden. In 2012, 29.1 million Americans were diagnosed with diabetes, up from 25.8 million in 2010, costing an estimated $245 billion in direct medical expenses and reduced productivity.[2] If not properly managed, the complications associated with diabetes progressively diminish overall health and can lead to comorbidities such as stroke, heart

(continued on page SP582)

Also in this issue...

Non-caloric artificial sweeteners

While artificial sweeteners have an established market, research studies point to their deleterious metabolic effects (SP568).

Bionic Pancreas

Research efforts of a scientist, and father of a T1DM patient, come close to fruition with the evaluation of the artificial pancreas in late-stage clinical trials (SP572).

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Partner of Center For Value Based Medicine®

Introducing Jardiance®

(empagliflozin) tablets 10 mg/25 mg

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

- Significant A1C reduction
- Once-daily oral dosing
- Additional benefit of weight loss*

* JARDIANCE is not indicated for weight loss. Weight change was a secondary endpoint in clinical trials.[1]

INDICATION AND LIMITATION OF USE

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

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

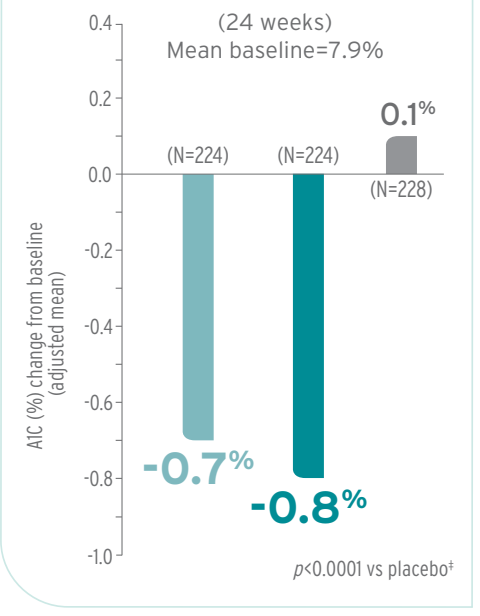
Boehringer Ingelheim

JARDIANCE is proven to significantly reduce A1C

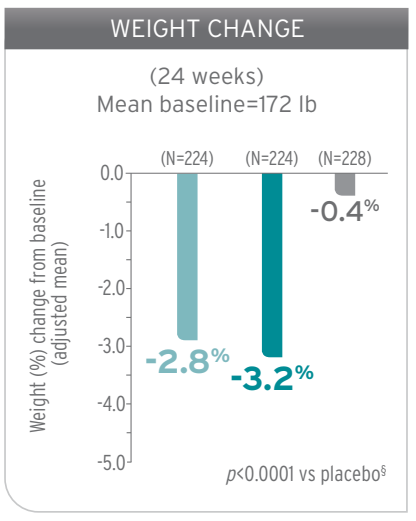
In addition to lowering A1C, JARDIANCE significantly reduced weight†

JARDIANCE monotherapy vs placebo (24 weeks)

A1C REDUCTION



WEIGHT CHANGE



■ JARDIANCE 10 mg ■ JARDIANCE 25 mg ■ Placebo

†JARDIANCE is not indicated for weight loss. Weight change was a secondary endpoint.[1]

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

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

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

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

‖JARDIANCE is not indicated as antihypertensive therapy. Blood pressure (BP) change was a secondary endpoint.[1]

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

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

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Hypotension

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

Impairment in Renal Function

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

Jardiance® (empagliflozin) tablets 10 mg/25 mg

Learn more at www.Jardiance.com

Lilly

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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

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

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

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

USE IN SPECIAL POPULATIONS

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

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

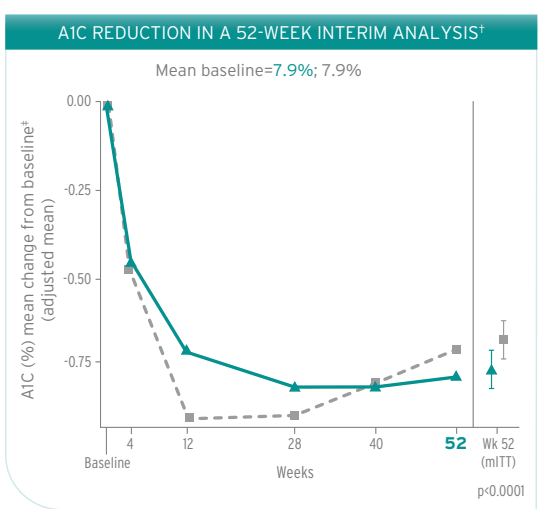
Geriatric Use
JARDIANCE is expected to have diminished efficacy in elderly patients with renal impairment. The incidence of volume depletion-related adverse reactions and urinary tract infections increased in patients ≥ 75 years treated with JARDIANCE.

JARPROFISI 8.2.14

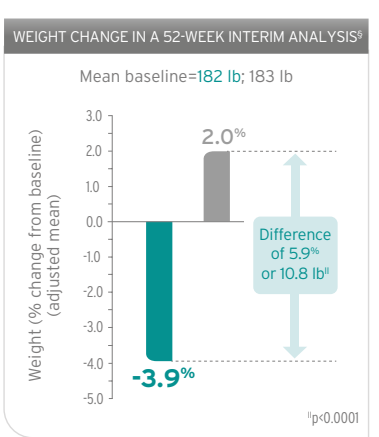
Boehringer Ingelheim

In adults with type 2 diabetes,

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



*JARDIANCE is not indicated for weight loss. Weight change was a secondary endpoint.[1]



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

†Completers only.

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

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

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

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

¶JARDIANCE is not indicated as antihypertensive therapy. BP change was a secondary endpoint.[1]

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

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

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

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

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

Jardiance® (empagliflozin) tablets 10 mg/25 mg

Lilly

JARDIANCE® (empagliflozin) tablets, for oral use ℞ only

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information.

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

CONTRAINDICATIONS:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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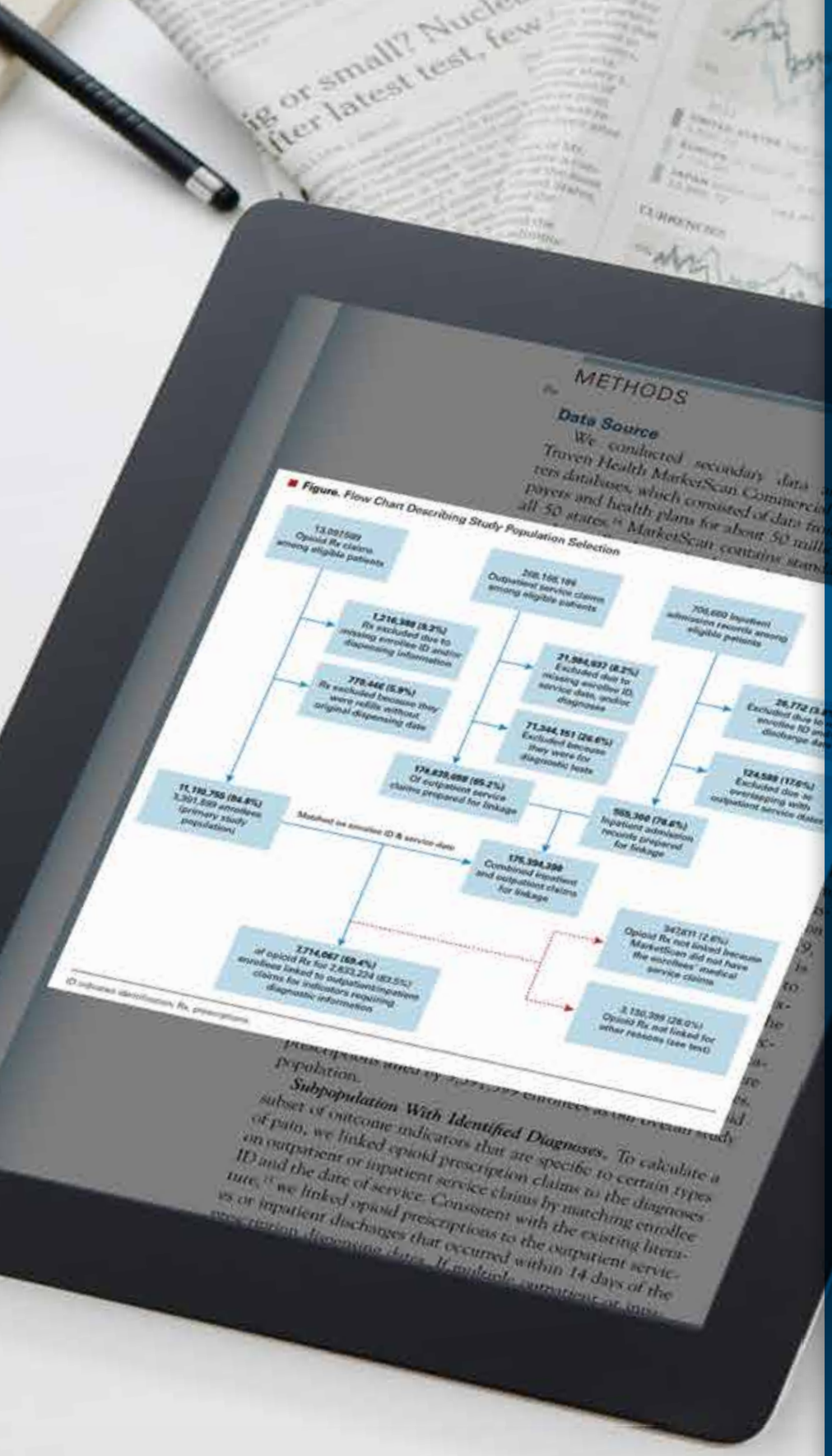

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For persons with diabetes, recovery from surgery is particularly complicated. Research has shown that insulin resistance could result from surgery, and its intensity could define the recovery period. These patients also face a greater risk of infection and wounds that do not heal, leading to other health problems and higher hospital costs.

"Many companies hesitate to tell workers about any job-related risks they're not legally obligated to disclose, which is self-defeating. You can't expect people to work hard to prevent serious health problems if they don't know they're at risk in the first place."

—Eric Dinenberg, MD, MPH
Chief Medical Officer
Viridian

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It's hard to believe that 2014 is drawing to a close. As you look ahead to the New Year, please plan to join us for our annual conference, Patient-Centered Diabetes Care, which will take place April 16-18, 2015. We're heading to Boston next year, so that we can present this essential multistakeholder meeting in partnership with the well-known Joslin Diabetes Center. Robert A. Gabbay, MD, PhD, the chief medical officer at Joslin who recently joined *Evidence-Based Diabetes Management* as our editor-in-chief, is already working with us to ensure an outstanding group of speakers and engaging panel discussions. This is an important time in diabetes care, as we have learned through our efforts with the AJMC ACO and Emerging Healthcare Delivery Coalition—doctors, hospitals, and health plans are focused on the quality measurements for diabetes that define not only how well patients are doing, but also how well care is being delivered. As we discuss in this issue, early data from the Pioneer ACOs raises questions on whether it's possible to deliver on all 3 parts of the "triple aim" at the same time, at least with diabetes. There's no doubt that these issues will be debated at this year's conference.

Our partnership with Joslin for Patient-Centered Diabetes Care reflects our shared understanding that building better lives for those with diabetes requires that we create opportunities for exchanges among those who have a say in how diabetes care occurs.

Our partnership with Joslin for Patient-Centered Diabetes Care reflects our shared understanding that building better lives for those with diabetes requires that we create opportunities for exchanges among those who have a say in how diabetes care occurs. That means bringing payers, providers, policy leaders, independent researchers, and leaders from the pharmaceutical sector together, both for shared learning opportunities and for networking. At *The American Journal of Managed Care*, we excel at these gatherings, and the feedback we receive is outstanding. This year, sessions will cover developments in clinical practice, in changing behavior, and in technology that can assist in healthcare monitoring, medication adherence, and in data collection and performance evaluation. We hope that our collaboration with an Joslin will see an increased participation by clinicians this year, as we strive to give you tools to both care for and motivate your patients. We believe this year's event will be our best ever, and we hope to see you in Boston.

Brian Haug
Publisher

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.

A new option for type 2 diabetes therapy starts here

Trulicity™ is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that 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 first-line therapy for patients inadequately controlled on diet and exercise. Has not been studied in patients with a history of pancreatitis; consider another antidiabetic therapy. Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. Not a substitute for insulin. Has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. Not for patients with pre-existing severe gastrointestinal disease. Has not been studied in combination with basal insulin.

Select Important Safety 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.

Please see Important Safety Information including Boxed Warning about possible thyroid tumors including thyroid cancer and Brief Summary of Prescribing Information on following pages.

trulicity™

dulaglutide injection once weekly

0.75 mg/0.5 mL, 1.5 mg/0.5 mL

A new once-weekly GLP-1 RA therapy is now approved[1]

Trulicity™ offers proven A1C reduction and once-weekly dosing in the Trulicity pen.[1]

Trulicity is a new option for adult patients with type 2 diabetes who need more control than oral medications are providing.[1]

To learn more about Trulicity, visit www.trulicity.com or contact your Lilly Account Manager.

Important Safety Information

WARNING: RISK OF THYROID C-CELL TUMORS

In male and female rats, dulaglutide causes 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.

Trulicity is contraindicated in patients with a prior serious hypersensitivity reaction to dulaglutide or any of the product components.

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.

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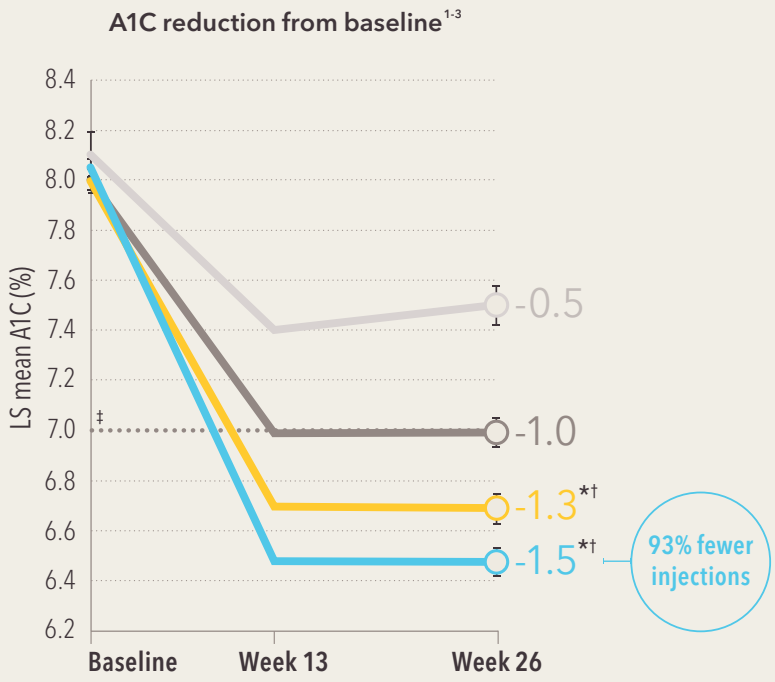
Once-weekly Trulicity showed significant A1C reduction[1]



- **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

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Additional information can be found at www.trulicity.com

DG HCP BS 18SEP2014

Trulicity™ (dulaglutide) HCP BS 18SEP2014

Patient Convenience, Value-Based Care, and Finding the Balance

Robert A. Gabbay, MD, PhD

We are pleased to bring you another issue of *Evidence-Based Diabetes Management*. Our healthcare environment continues to evolve, and in this issue we highlight a potentially revolutionizing innovation that is occurring nationally: retail clinics. Clearly, they are here to stay, based on growing consumer demand. The question is, how do we optimize this care model and ensure coordination with traditional elements of the healthcare system? Optimally, meeting patient demand for greater access and convenience can be married with the best elements of our current healthcare system in a coordinated fashion.

This issue highlights several controversies in scientific literature. There continues to be debate on the role of artificial sweeteners and their metabolic impact, especially in diabetic patients, as was highlighted in a recent study published in the journal *Nature*. Examination of the biological impact of noncaloric artificial sweeteners identified glucose intolerance—a result of an alteration in the intestinal flora. As the search for a greater understanding of the causes of type 1 diabetes mellitus (T1DM) continues, potential environmental triggers have been ardently studied based on evidence that only 50% of the risk for the development of T1DM is genetic. A variety of viruses have been implicated, and new epidemiologic work in Taiwan continues to raise the specter of enterovirus, although numerous other studies have suggested otherwise.

As we move toward a more value based healthcare system, appropriate methods to measure quality of care are critical. Accountable care organizations (ACOs), as envisioned by CMS, have outlined some diabetes measures, while at the same time the National Quality Forum and others find a compendium of diabetes quality measures. The historic challenge in defining these measures is the movement toward more individualized care goals for patients with diabetes. What remains frustrating for many clinicians is balancing individualized goals, as recommended by the American Diabetes Association and others, with the need for population management and metrics to drive ACO goals. The hope is that with more robust data, one can incorporate other factors (ie, diabetes comorbidities) to develop more sophisticated measures of clinical quality that resonate with evidence-based care and clinical judgment.

Robert Gabbay, MD, PhD

Robert Gabbay, MD, PhD, editor-in-chief of *Evidence-Based Diabetes Management*, is chief medical officer and senior vice president of Joslin Diabetes Center. **EBDM**

Call for Papers

The US National Library of Medicine defines evidence-based medicine as "the process of systematically finding, appraising, and using contemporaneous research findings as the basis of clinical decisions. Evidence-based medicine asks questions, finds and appraises relevant data, and harnesses that information for everyday clinical practice."

On this basis, *Evidence-Based Diabetes Management* seeks high-quality commentaries and original research reports on cutting-edge clinical, pharmacoeconomic, and regulatory topics in diabetes care. The objective is to provide patients, clinicians, payers, health plans, and the pharmaceutical community, evidence-based information to aid care decisions. The editors are especially interested in papers that promote dialogue and facilitate communication among stakeholders and healthcare policy makers that would potentially impact the efficiency and outcomes in cancer care. *Evidence-Based Diabetes Management* regularly publishes articles that cover:

- Drug pipelines
- Clinical trial results
- Diagnostic advances
- Health policy (private, Medicare, and Medicaid)
- Regulatory policies

We would like to highlight that *Evidence-Based Diabetes Management* would be an ideal platform to publish "orphan scientific findings," which may be important but not extensive enough to support a complete article for publication in a peer-reviewed journal.

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If you wish to submit to *Evidence-Based Diabetes Management*, or have further questions, please contact:

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Are Low-Cal Sweeteners at the End of Their Game?

Surabhi Dangi-Garimella, PhD, and Sejal Saraiya, PharmD

Advertisements are full of claims for sweeteners being "natural" or "no-calorie" replacements for sugars that can help support a healthy lifestyle. These products would seem to be ideal alternatives for a person with hyperglycemia: a sweetener minus the carbohydrates and the accompanying calories. But promotions don't tell the full story, as a study by Suez et al, published in the journal *Nature,* discovered. Some of these noncaloric artificial sweeteners (NAS) can alter the intestinal microbiome, leading to glucose intolerance.[1]

Table. FDA and GRAS Approved Artifical Sweeteners and Brands[2,3]

Sweetener	Approval Date	Sweetness Factor (Relative to sugar)	Product(s)
Saccharin	1958	200-700 times	Sweet'N Low, Sweet Twin, Sugar Twin
Aspartame	1981	200 times	Nutrasweet, Equal
Acesulfame potassium	1988	200 times	Sunett, Sweet One
Sucralose	1998	600 times	Splenda
Neotame	2002	8000 times	Newtame
Advantame	2014	20,000 times	N/A
GRAS Approved Artificial Sweeteners[2,3]			
Stevia/Rebaudioside			A Sweet Leaf, Sun Crystals, Steviva, Truvia, PureVia
Extracts from Swingle fruit/monk fruit			N/A

GRAS indicates generally recognized safe.

What Has the FDA Approved?

Thus far, 6 artificial sweeteners have been sanctioned by the FDA (see **Table**): acesulfame potassium, aspartame, saccharin, sucralose, neotame,[2] and most recently, advantame.[3] Because they are not metabolized by the body, they do not add calories to a drink or food item. However, the additives in these products can add to their calorie and sugar content.[2]

Health Effects of Artificial Sweeteners

In the study by Suez et al, the authors, most of whom are at the Weizmann Institute of Science in Israel, fed an NAS supplement (saccharin, sucralose, or aspartame) to mice, and observed a significant increase in their blood glucose levels compared with the control mice, which consumed sugar.[4] This pattern was observed in mice fed a normal diet as well as in those fed a high-fat diet (obesity model). The role of the gut flora in regulating blood sugar levels was then confirmed by 2 separate experiments:

- treatment with antibiotics purged NAS-induced glucose intolerance, in both diet groups;
- transplanting feces from NAS-fed mice to germ-free mice changed the composition of their gut microbial flora and elevated their blood glucose levels as well.[4]

Using the paradigm of the mouse model, the authors replicated their experiments in 400 human subjects and discovered differences in the patterns of microbial flora expressed in the gut of NAS consumers, along with an increase in their blood sugar levels. A high-NAS diet in 7 trial participants confirmed the hypothesis: just 4 days into a 7-day experimental period, 50% of participants possessed altered bacterial composition and elevated blood glucose levels.

Thus, this study by Suez et al confirmed that the same artificial sweeteners that are advertised to overweight consumers as a tool to help them lose weight may actually contribute to or worsen the condition of individuals with metabolic abnormalities, such as diabetes and obesity.[4]

Taking this a step further, David L. Katz, MD, MPH, FACPM, FACP, director, Yale University Prevention Research Center, wrote in an article, "Is it possible that chemicals in our food, to which we of course have no native adaptations, are contributing to some or all of the subtle but indirect harms? The precautionary principle argues that we don't assume something is entirely safe just because we don't have proof that it's dangerous. These are chemical compounds, not food, and we know our native diet was made up of food."[5]

Old Story, New Headline

These results are not at all a surprise. Back in 2008, researchers fed the sweetener Splenda—composed of sucralose, maltodextrin, and glucose—to rats for 12 weeks, and analyzed their gut microbes as well as expression of 2 enzymes: a membrane efflux transporter, P-glycoprotein, and a metabolizing enzyme, cytochrome P-450. The 2 enzymes play an important role in restricting the bioavailability of oral drugs. Along with changes in the microbial composition, Splenda increased the expression of both enzymes at the end of the 12-week period.[6] (*Note:* the changes noted were at FDA-approved levels of sucralose.)

The debate on the health effects of one of the earliest NASs, aspartame, lingers today. While the *Nature* paper drew attention to the metabolic effects of aspartame, this popular NAS has previously been shown to be a cause of cancer,[7] developmental deficits, and neuronal toxicity.[8]

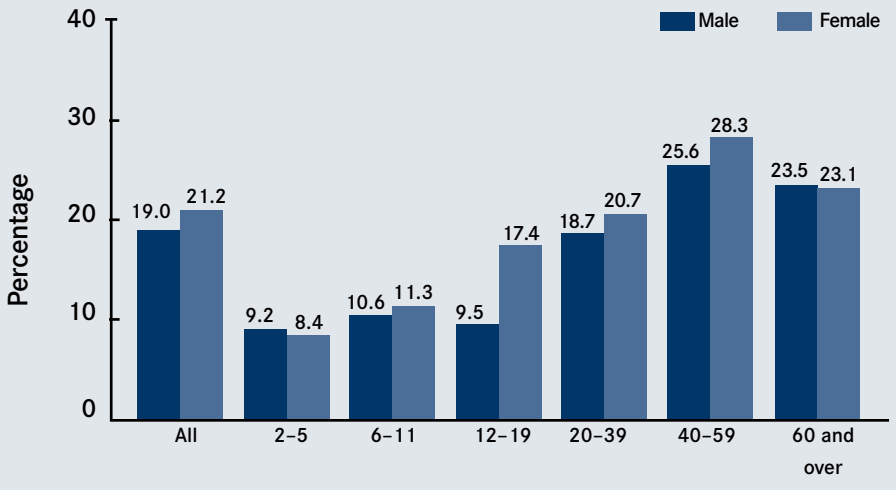
More Common Now Than Before

Bread, cereal, soda, canned products, jams and jellies, fruit spreads, dried fruits, chewing gum, candy, dairy-based drinks and desserts, sauces, soups and broths, flavored drinks…name the product, and it's easy to find an artificial sweetener in the ingredients.[9] Despite all the evidence on the health effects of NAS, their use has not dwindled.

Between 1999 and 2004, a significant increase in the number (more than 6000) of food products claiming to be noncaloric—containing artificial sweeteners—was noted. According to the National Household Nutritional Survey, as of 2004, about 15% of the population in the United States regularly used artificial sweeteners.[10] The addiction of the population to diet drinks is highlighted by a data brief released by the CDC's National Center for Health Statistics. Between 2009 and 2010, 20% of the population in the United States 2 years and older consumed diet drinks (see **Figure 1**).[11] Many individuals with diabetes commonly use artificial sweeteners as an alternative to sucrose.[12] With the high incidence of diabetes—29.1 million people, or 9.3% of the population, as of 2012—an increased vigilance on the impact of these sweeteners is essential.

The obesity epidemic in the United States, which has affected one-third of the adult population,[13] points to sugar and other caloric sweeteners as the primary culprits,[10] and has led to an increase in the utilization of weight loss products, including sweeteners.[14] Often, individu-

Figure 1. Percentage of Population 2 Years and Older Who Consumed Diet Drinks on a Given Day: United States, 2009-2010[10]



The Sugar-Sweetened Beverage Debate

The Rudd Center for Food Policy and Obesity at Yale released a policy brief in 2012 that recommended beverage taxes for sugar-sweetened beverages (SSBs).[1] Considering the high-calorie, zero-nutrition nature of these drinks, the Center's recommendation is a win-win: a check on the population's nutrition intake, increased revenue for health programs, and a likely reduction in the medical and insurance costs of diet-related diseases.

Policies enacted by European nations—Denmark, Finland, France, and Hungary—caused 34 states within the United States and the District of Columbia to follow suit by enforcing a soda tax (see **Map**), according to a research report filed by Bridging the Gap, a program funded by the Robert Wood Johnson Foundation. This is a sales tax levied on the sale of SSBs in food stores and in vending machines. The report states, however, that these sales taxes are too small to have a huge impact (30 states charge <7% in taxes), and so policy makers are looking into the use of excise taxes, with dedicated revenues for public health programs.

A national tax of a penny per ounce on SSBs generated an estimated $13 billion in 2013. The report estimates that in the 3 states with the highest obesity rates, Mississippi, Louisiana, and West Virginia, the tax would raise $136 million, $210 million, and $84 million in revenue, respectively.

The city council of Berkeley, California, took a step in this direction in its recent midterm elections, including the City of Berkeley Sugary Beverages and Soda Tax, Measure D, on the election ballot on November 4. While it won the vote of 75% of citizens,[2] a similar measure in San Francisco—the City of San Francisco Sugary Drink Tax, Proposition E—won a simple majority, but not the two-thirds needed for adoption.[3] What's next? Some public health advocacy experts believe that this movement is a step in the direction toward a national tax on SSBs, while others think that warning labels are the next thing coming.

Meanwhile, efforts are ongoing to put this discussion on a national stage. In July of this year, US Rep Rosa DeLauro (D-CT) introduced the Sugar-Sweetened Beverages Tax (SWEET), which would charge an excise tax of 1% per teaspoon of caloric sweeteners and thus add 9 cents to the cost of a 12-ounce can of soda,[4] directly impacting the manufacturing cost. **EBDM**

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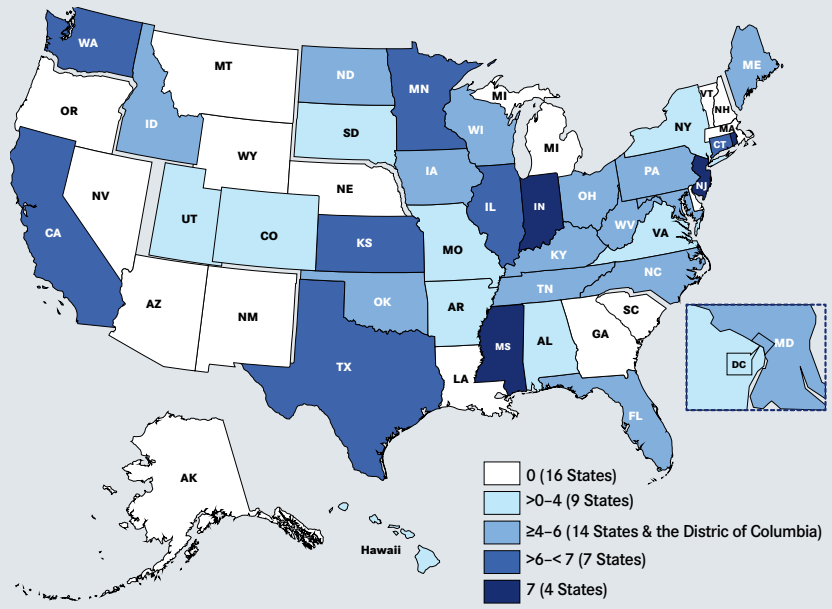
Figure 2. Sales Tax on Regular Soda Across States (as of January 1, 2014)



Does not include rates for 3 states with mandatory Statewide local sales taxes: CA (1%), UT (1.25%), and VA (1%). The following states also impose additional, non-sales taxes on regular soda: AL, AR, RI, TN, VA, WA,WV.

Source: Bridging the Gap Program, University of Illinois at Chicago, 2014.

als who are weight conscious consider artificial sweeteners "healthy," despite several large studies indicating the opposite. Preload experiments have found that human appetite is enhanced by sweet taste, whether it be from sugar or artificial sweeteners, while studies in rats identified an increased weight gain along with an elevated total energy intake when supplemented with saccharin compared with glucose.[10]

Global Market Access

A research report evaluating market penetration of sweeteners, published by Mintel and Leatherhead Food Research, has reported that stevia, the natural, plant-based sweetener, is gaining a lot of traction with consumers and nudging more established sweeteners, like aspartame, from their pedestal. Stevia was valued at $110 million in 2013—based on its global use in the food and beverage industry—a number expected to escalate by 2.5-fold by the year 2017 to $275 million. Aspartame, which held a market share of $437 million in 2013, is likely to plummet to $328 million by 2017, as stevia and acesulfame K grow more popular.[15]

The numbers estimated in the report underscore the popularity of these intense artificial sweeteners in the food and beverage industry. A 2.8% increase from 2012 to 2013, saw the global sweetener market reach $1.27 billion, and it is predicted to reach $1.4 billion by 2017, an almost 10% spike.[15]

Wrote Katz in his blog on LinkedIn, "Neither the current excess of sugars, nor the sugar substitutes that foster a sweet tooth and disrupt the microbiome," is an answer to our problem. "There may be better options in the pipeline, namely non-caloric sweeteners that don't exert unintended harms. Both stevia and monk fruit extract look promising at this point, but we need more data."[16]

If these estimates are to be believed, they imply that the use of artificial sweeteners is on the rise, despite all the controversial research reports on their health outcomes. But then, you have people who believe sugar is a carcinogen. So it just depends on where your interests lie! **EBDM**

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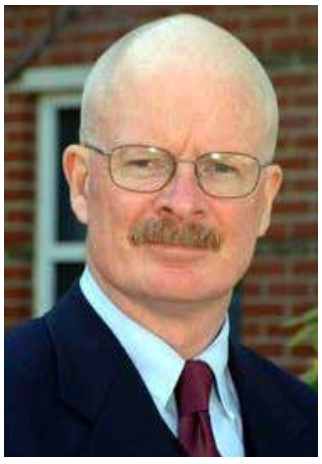
Can Psychiatrists Fill a Medical Gap for Those With Diabetes and Mental Health Issues?

Mary K. Caffrey

In the general population, it can be hard to get anyone with diabetes or obesity to stick with taking medication, to quit smoking, or to follow a diet and exercise plan. Add a serious mental illness to the mix, and the challenge escalates—so much so that persons with both diabetes or obesity and a serious mental illness, such as schizophrenia, die 15 to 20 years earlier than those without mental illness, or it's comorbid medical conditions, according to Joseph P. McEvoy, MD, of the Medical College of Georgia at Georgia Regents University.

McEvoy's stark assessment came during his presentation, "Managing Modifiable Risk Factors for Cardiovascular Disease and Cancer in Individuals With Serious Mental Illness," which was part of the US Psychiatric and Mental Health Congress held September 20-23, 2014, in Orlando, Florida.

However, McEvoy's reality check came with an intriguing solution for treating chronic conditions among the mentally ill: can psychiatrists provide basic primary care for high blood pressure, weight control, or smoking cessation until they can get their patients to a clinic or a specialist? "My hope is that some subset of mental health prescribers will be willing to take this on," McEvoy said.



Joseph P. McEvoy, MD

Those who don't have mental health issues can find the medical system in the United States difficult to engage; it's especially imposing on those who suffer depression or cognitive deficits that come with serious mental illnesses. Individuals covered by insurance may not have transportation to reach a provider, and they may not trust a new provider. Additionally, complications associated with mental illness make it harder for patients to understand or follow instructions.

So, trying to address high blood pressure, alcohol abuse, risky sex, or heavy smoking among this group will require solutions that "do not depend on *them*," McEvoy said. "We know exactly what is causing this accelerated mortality. There are no mysteries here." Among his recommendations:

- Psychiatrists, at least some of them, must reorganize their practices to provide basic primary care services where patients already feel comfortable and safe.
- The use of nurse care managers is essential to help connect patients with services and stay in touch with family members who can aid in transportation and care.
- Psychiatrists must connect their patients with smoking cessation services and counsel them about reducing sun exposure.
- Psychiatrists must rethink the use of certain medications that cause weight gain and increase cardiometabolic risk, unless those therapies are absolutely necessary.

A conference attendee pointed out several obstacles to McEvoy's approach: will payers fund this? Can nurses with bachelor's degrees run smoking cessation groups, or act as navigators? Is a master's degree necessary? McEvoy agreed that reimbursement can be a challenge, and that he hopes payers see that it makes sense to use master's-educated personnel for higher-level tasks, such as coordinating with primary care physicians.

One key is understanding that some of the mentally ill suffer serious cognitive impairment, which McEvoy said may be "up to 1.5 standard deviations to the left" from a healthy control. This makes taking instructions for exercise and especially diet exceedingly hard, and requires strong support from family members or others in the patient's social circle. But that is complicated, too. Persons with serious mental illness tend to have problems forming attachments to others, and McEvoy said studies show this is a strong predictor of how well patients do with diabetes care.

A reason that the "team" approach for diabetes intervention works, he said, is that 60% to 70% of patients will respond when they know a group is invested in their health. For those with serious mental illness, the numbers are reversed.

"The slightest hiccup will cause them to drop out," he said. "They don't play well on the team, even if the purpose of that team is to keep them alive."

However, integrating medical care with mental health services has shown some success. The closer the medical services were to the mental health services, the more likely patients were to use them, according to a Veterans Administration study. "Even a short journey to a free clinic was associated with less use compared with bringing the primary care service to the mental health clinic," McEvoy said.[1]

He believes that if a small group of psychiatrists were willing to develop a competency in treating diabetes, hypertension, and obesity, it could allow the healthcare system to focus medical efforts on those mentally ill patients with more complex medical issues. However, he cautioned that psychiatrists should not try to treat those with inadequate renal function or reproductive problems.

He then provided some examples of basic prescribing protocols for common medical problems:

- ***Elevated low-density lipoprotein-cholesterol.*** For those with LDL cholesterol greater than 130 mg/dL, excluding women of child-bearing potential not on birth control. Prescribe simvastatin, starting at 10 mg every night at bedtime (QHS) and increase at monthly intervals until the patient is at target, with a maximum dose of 40 mg. Patients should be monitored for a small risk of liver damage or muscle breakdown.

- ***Hypertension.*** Exclude those with chronic kidney disease that has progressed beyond stage 1; glomerular

Lurasidone's Effect on Comorbidities Explored

Mary K. Caffrey

In June 2013, the FDA expanded its indication for the antipsychotic lurasidone, marketed as Latuda, for use in bipolar disorder, either as a monotherapy or in combination with lithium or valproate. (It was first approved for schizophrenia.)[1]

Henry Chung, MD, and Joseph Calabrese, MD, director of the Mood Disorders Program at University Hospitals Case Medical Center, Case Western Reserve School of Medicine, presented data on lurasidone, September 22, 2014, during the US Psychiatric and Mental Health Congress in Orlando, Florida. Their presentation was sponsored by Sunovion Pharmaceuticals.[1]

Lurasidone has been praised in some circles for its relative safety and especially for its lack of adverse cardiometabolic effects, although the FDA does not permit Sunovion to specifically market this aspect. However, in April 2014, writer David Allen, MD, noted that while the drug was superior to other antipsychotics in terms of cardiometabolic effects, the fact that Sunovion had sought FDA approval to prove its effects on bipolar depression did not mean that makers of other, less expensive drugs in the same class would not do the same thing.[2]

In his portion of the presentation, Chung outlined the toll that bipolar depression takes on patients in terms of lost productivity and costs to the healthcare system. He presented data showing that direct and indirect costs of the disease were $151 billion in 2009. Reducing episodes of depression in these patients, he said, has the potential to trim their overnight hospital stays, visits to the emergency department, and other costs to the system.

The comorbidities associated with severe mental illness are gaining more attention, Chung said. As community health clinics have begun to integrate primary medical care into their services under healthcare reform, there has been an increase in the awareness of the overlay between mental illness and cardiovascular conditions, including the number of mental health patients who have heart attacks, he said.

A patient's overall cardiometabolic profile would be a consideration for how long a patient might remain on lurasidone, in addition to how well the drug is helping with symptoms of depression. "At no time have we had more incentive to look at both things together," he said. **EBDM**

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filtration rate less than 90 mL/min. The target systolic blood pressure is less than 140 mm Hg. Start with hydrochlorothiazide 12.5 mg QHS; the dose can be increased to a maximum dose of 25 mg QHS at monthly intervals or until the target is reached. Doctors can prescribe amlodipine, starting at 5 mg QHS and increasing in 2.5-mg increments to a maximum dose of 10 mg QHS or until the target is reached.

- ***Non–insulin-dependent type 2 diabetes mellitus.*** Exclude those with renal impairment (serum creatinine greater than 1.5 mg/dL for men; greater than 1.4 mg/dL for women) or acidosis (serum bicarbonate less than 23 mEq/L). Start metformin 250 mg twice daily, and then increase dose to 500 mg twice daily (with meals). Recheck glycated hemoglobin after 2 months. **EBDM**

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ACO Results

Among ACO Pioneers, Data Reveal Diabetes Performance Paradox

Mary K. Caffrey

For accountable care organizations (ACOs), the holy grail of performance is the triple aim of delivering better population health with greater patient satisfaction while achieving financial savings. But can all 3 be achieved at once?

That's the question experts were anxious to find out in early October. For the first time, CMS released detailed financial and quality performance data from the first 2 years of the program for the Pioneer ACOs. The original Pioneers were 32 healthcare groups selected to test value-based reimbursement principles because of their experience in this area. That the number of Pioneers dropped to 23, and then to 19, was an early sign that achieving the triple aim might be more attainable in theory than in practice.[1]

A closer look at the CMS data reveals that diabetes care, in particular, presents a paradox: in general, ACOs that scored higher in helping patients achieve diabetes health targets had modest financial performances.[2] Conversely, some ACOs with stronger financial performances rated in the lower half of the diabetes scores.

Helping patients with diabetes mellitus (both type 1 and type 2) achieve goals in blood pressure, glycated hemoglobin (A1C), and cholesterol, and maintain positive lifestyle habits is key to preventing more costly care over the long term. In fact, 6 of the 33 quality measures now used by CMS to determine Medicare reimbursement are related to diabetes, 5 of which make up a "diabetes mellitus composite." Those 5 measures are:

- the percentage of patients 18 to 75 years of age with diabetes mellitus who had A1C <8.0%
- the percentage of patients 18 to 75 years of age with diabetes mellitus who had low-density lipoprotein control of <100 mg/dL
- the percentage of patients 18 to 75 years of age with diabetes mellitus who had a blood pressure <140/90 mmHg
- the percentage of patients with a diagnosis of diabetes who indicated they did not use tobacco
- the percentage of patients 18 to 75 years of age with diabetes mellitus and ischemic vascular disease with documented daily aspirin use.[3]

While these 5 elements are measured as percentages, the composite is listed in CMS data as a score; the average among the Pioneers for the second year (2013) was a 33.26.[2] In 2013, among the top 6 ACOs in the diabetes composite score rankings, only Mount Auburn Cambridge Independent Practice Association saw a financial savings above 3%; this ACO saved 3.3%, or $3.6 million. The next best financial performance among ACOs with high diabetes scores was a savings of 2.6%, or $3.12 million, for Park Nicollet Health Services. (See **Table**.)[2]

On the flip side, the Pioneer ACO with the best financial performance, both on a percentage basis and in the dollar among of savings, was Montefiore. The ACO saw a year 2 savings of 7%, or $24.59 million. However, its diabetes composite was on the lower end of the Pioneers at 22.93, with only 4 groups scoring lower.[2]

Other ACOs with better-than-average financial results repeated the pattern: Monarch HeatlhCare saved 5.4%, or $14.61 million, but had a diabetes composite of 23.98; Steward Healthcare Network's savings was 3.3%, but a more substantial $19.22 million overall, while its diabetes score was 28.46; and Beth Israel Deaconess Care saved 3.9% or $17.38 million, yet its diabetes composite was still below average at 30.90.[2]

Policy researchers were eager to dig into the data when it was unveiled in October, and will likely continue to look for factors, such as the makeup of the population or the scalability of ACO programs, to explain the disconnect between the diabetes scores and financial results.

An analysis from experts at the Brookings Institution, that appeared shortly after CMS released the data, noted that while all but 1 of the ACOs still in the program improved quality from 2012 to 2013, a troubling bifurcation between 2 types of Pioneers was emerging.[4]

"After year 2, there still does not appear to be a direct relationship between higher quality scores and level of savings or losses in the Pioneer Program," said the authors, led by S. Lawrence Kocot, JD.[4]

For its part, Montefiore ACO is working hard to improve the measures that make up the diabetes composite, according to spokeswoman Tracy Gurrisi. A number of patients with comorbidities within the ACO's population are definitely a factor, she said, noting that Montefiore's composite improved from 2012 to 2013.

"To help address barriers like access to care and education about diabetes, we started hosting a series of Diabetes Day programs at Montefiore sites that target patients with poor diabetes control," Gurrisi said.

"At Diabetes Day programs, patients are able to receive a range of necessary exams in a single location as well as receive education about self-management. Days include diabetic care appointments with primary care, specialists like nutritionists and ophthalmologists, and diabetic educators so patients see all providers in one location at one time. This tactic will enable immediate treatment or intervention when providers identify a need, instead of referring patients for future appointments." **EBDM**

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Table. Year 2 Results for Pioneer ACOs: Comparing Diabetes Care Quality, and Financial Performance

Top Pioneer ACOs for DM Scores	2013 DM Composite	2013 Savings/Loss %	2013 Gross Savings/Loss
Park Nicollet	56.07	2.6	$3.12 million
Allina	51.07	1.7	$1.87 million
Fairveiw Health Services	48.46	Deferred to 2014	Deferred to 2014
Bellin-ThedaCare Healthcare	48.33	2.1	$3.21 million
Mount Auburn Cambridge	47.18	3.3	$3.6 million
Atrius Health	46.1	1	$3.15 million
Top Pioneer ACOs for Savings			
Montefiore	22.93	7	$24.59 million
Monarch	23.98	5.4	$14.61 million
Steward	28.46	3.3	$19.22 million
Banner	28.07	2.8	$15.15 million
Beth Israel Deaconess	30.9	3.9	$17.38 millon
PIONEER AVG	33.26		

Source: CMS.gov website.
ACO indicates accountable care organization; DM, diabetes mellitus.

The Bionic Pancreas: Getting Closer to Reality

Andrew Smith

Many months typically elapse between fresh announcements about the "bionic pancreas" developed at Boston University (BU) and Massachusetts General Hospital (MGH), but the process of testing and refining the technology proceeds steadily. Indeed, one of the researchers who leads the project recently outlined the long series of successes that have brought the experimental system to the threshold of final-stage clinical trials, and suggested that it may even reach the market a little earlier than initially expected.

"We hope to be moving to pivotal studies in 2015, where we use a fully integrated device that has both an insulin pump and a glucagon pump, the continuous glucose monitor receiver, and the bionic pancreas algorithm, in a single device," said Steven Russell, MD, PhD, assistant professor at Harvard Medical School and attending physician at MGH, in a webinar.[1] "Once we finalize that design, we're going to start the pivotal studies, and we hope to submit a premarket approval application to the FDA by late 2016 or early 2017, which means that we could commercially launch the device as early as 2017."

Steven Russell, MD, PhD

Russell began his webinar by emphasizing that people with type 1 diabetes mellitus (T1DM) today have already benefitted from a true revolution in care. Until 1922, when researchers discovered how to purify insulin from animals and use it to combat diabetes in humans, T1DM was a relatively speedy death sentence. The best available treatment was virtual starvation, but the technique only extended lifespan modestly, and it reduced patients to living skeletons.[2]

Insulin represented such a monumental improvement over the *status quo*, Russell said, that medical authorities wrongly considered diabetes to be all but cured. The bionic pancreas may not be a breakthrough on par with insulin, but if it works as well in real life as it has in tests, it could produce the biggest revolution in T1DM care since Calvin Coolidge became president.

Russell predicted that the system will virtually eliminate hospitalizations and other short-term complications from hypoglycemia, while simultaneously reducing the long-term complications of excessive blood sugar by more than 80%. This alone would be great news for people with T1DM, a disease that continues to be the nation's leading cause of blindness, kidney failure, and nonemergency amputations, despite incremental advances in care since the advent of insulin therapy.[3]

For many patients, however, the best news about the bionic pancreas may be the instructions for using the machine: calibrate the glucose monitor twice a day and ensure that the system is stocked with insulin, glucagon, and batteries. That's it. Patients can inform the device that they're about to eat a meal or snack, but they don't have to. The only vital patient information that the system needs is their weight.

A number of teams around the world, including academic groups in Europe and at the University of Virginia, are working on similar technology. All seek to automate the task of blood sugar control as much as possible by combining continuous glucose monitors (CGMs) with insulin pumps, computer analytics, and various other elements.[4] Despite the basic similarities, all of these experimental devices differ somewhat. The bionic pancreas from the team at MGH and BU automates the process of increasing blood sugar, as well as the process of decreasing it, by administering both glucagon and insulin.

The size and shape of the team's bionic pancreas has changed dramatically since human trials began in 2008. Back then, the system paired a full-sized laptop with the wireless transmitters that BU engineers attached to standard hospital glucose monitors and pumps for the insulin and glucagon. Today's version combines a modified iPhone with a small glucose monitor and 2 pumps, each of which is just a bit larger than a pack of playing cards. The commercial model will likely pair each user's existing smartphone with a single box that combines the monitor and the 2 pumps.

The algorithm that drives the system has also advanced throughout the years, but the technology has maintained the same fundamental advantages over self-medicating humans. Machines effortlessly avoid the sort of mathematical errors that people make when they're calculating insulin dosages and timing. They also work more diligently than any human can.

Indeed, Russell said, most people with T1DM struggle with recommendations such as, that they stop 10 times a day to note their blood sugar and consider making adjustments. The artificial pancreas, on the other hand, notes blood sugar levels and considers adjustments 288 times per day, every day, forever. It catches problems far faster than people can, and uses very small doses of insulin and glucagon to fine-tune blood sugar very frequently.

These advantages have allowed the bionic pancreas to produce excellent results in trials to date, even as the development team has increased trial durations and reduced restrictions on patient behavior.

The first trial[5] recruited 11 subjects with no endogenous insulin secretion for a series of 27 hour-long experiments undertaken at a hospital. Each subject had 3 carbohydrate-rich meals during the course of the experiment, but for 6 of the subjects, the system immediately achieved a mean blood glucose concentration of 140 mg/dL, which meets the ≤154 mg/dL target from the American Diabetes Association. When the study team adjusted the algorithm's pharmacokinetic parameters to account for the varying speed of glucose absorption, the bionic pancreas got all 11 into the target range.

The second trial[6] tested the system twice for 51-hour periods in 6 subjects, who, again, ate high-carbohydrate meals and exercised. Overall, the mean plasma glucose was 158 mg/dL, with 68% of glucose values in the range of 70 mg/dL to 180 mg/dL. Hypoglycemia, defined as blood glucose less than 70 mg/dL, occurred only 8 times during the 576 hours of closed-loop blood sugar control, and accounted for just 0.8% of all the time that patients were using the system. Patients who medicate themselves often spend more than 10% of their lives in a state of hypoglycemia.

The so-called Beacon Hill Study of 2013 expanded the study period to 5 days, let patients leave the hospital and roam central Boston (with nurses shadowing them), and observed how patients fared with the bionic pancreas compared with a similar 5 days under their own care.[7] After giving the system 1 day to adjust to each patient, mean glucose levels fell from 159 mg/dL when patients cared for themselves to 133 mg/dL when they used the bionic pancreas. The percentage of time patients had glucose levels below 70 mg/dL fell from 7.3% to 4.1%.

The summer camp study of 2013 tested the bionic pancreas against normal care for 5-day periods in 16 boys and 16 girls, 12 to 20 years of age.[7] Mean glucose levels for the children, who were all attending special summer camps, were 158 mg/dL under normal standards of care and 142 mg/dL with the bionic pancreas (after the 1-day adjustment period). The time spent with low glucose levels fell from 7.6% to 6.1%, and the frequency of interventions for hypoglycemia fell from 1 per 0.8 days to 1 per 1.6 days.

The development team is currently analyzing results from 2 more studies: a 2014 summer camp study that tested the bionic pancreas on children as young as 6 years of age, and a 2-week long home trial in 48 adults at 4 sites around the country: MGH, Stanford University, the University of North Carolina at Chapel Hill, and the University of Massachusetts.

The home-use trial places a few restrictions on participants—like asking them not to leave the metropolitan area around each participating hospital—but otherwise asks them to live normally. Researchers do not receive any information from their devices during the course of a study unless a machine breaks or the patient's blood sugar gets dangerously low.

Until very recently, the bionic pancreas from Boston had a major weakness that struck some observers as the sort of critical flaw that might prevent it from ever achieving widespread usage: every commercially available glucagon formulation deteriorated so rapidly that users would have to mix it up and restock their machines every day. In recent months, however, a company called Xeris has begun providing the project with an experimental nonaqueous form of glucagon[8] that lasts for months and has performed, in tests to date, almost identically to fresh glucagon from Eli Lilly. Now, Russell said during his presentation, several other companies are working on similar formulations, so users of the artificial pancreas should benefit from price competition. Russell believes that the advent of a more stable form of glucagon makes the use of the hormone an unquestionable advantage for his team's bionic pancreas.

Systems that primarily use insulin have no way of raising blood sugar levels, which often fall below the desired level when people exercise, accidentally use too much insulin, or go too long without eating. Those single-hormone systems, therefore, must sound an alarm when glucose levels begin to fall and urge users to eat some form of sugar, even if it means

waking them up from a sound sleep. The bionic pancreas simply releases a bit of glucagon into the bloodstream, and the user never knows. Indeed, Russell said, the 2-hormone design of his team's device is a necessary precondition for making it operate like a real pancreas, which also secretes both insulin to lower blood glucose levels and glucagon to raise them.

Another potential concern that came up during the question-and-answer session following Russell's presentation was the risk that users would develop tolerance to glucagon if they received dozens of small infusions of the hormone every day.

Russell said that patients who participated in trials so far had shown no signs of developing any such tolerance. He then added that while future trials would certainly look for indications that people might develop glucagon tolerance over longer time frames, the chance of such a problem occurring appears remote, both because the body typically uses that hormone to boost blood sugar over the course of a lifetime and because of the very small doses involved.

Russell went on to note that the bionic pancreas typically uses far less insulin per day than patients use on their own, and when raising glucose levels, it typically uses far less glucagon than patients use sugar. Better still, he said, patients who use the bionic pancreas may well spend so little time with low blood sugar levels that they regain the hypoglycemic awareness that people with T1DM typically lose, thus developing an extra safeguard against the condition.

To date, bionic pancreas systems have worked reliably, and the team behind the technology believes not only that their creation will prove durable in real life, but also that it employs enough safeguards to give patients plenty of warning should any problems arise. The only real danger, Russell said, lies in the calibration of the glucose monitor: if patients calibrate it badly enough, they risk problems.

Russell concluded his presentation by addressing 1 other serious concern that haunts every potential medical breakthrough: price. Russell predicted that the bionic pancreas will likely cost more than a top-of-the line insulin pump—but not that much more. He also predicted that every insurance program would happily cover the device.

"It will incorporate 2 pumps, the CGM, the bionic pancreas algorithm, and a dual infusion set. We don't know what it will be priced at, but I would guess not double what an insulin pump costs," said Russell, who added that the cost to most patients would be low or nonexistent because insurers would have so much incentive to promote usage.

"The biggest cost of diabetes care is treating the complication. There also is a tremendous cost of hospitalizations due to severe hypoglycemia," Russell said. "We believe the system would be able to eliminate almost all those hospitalizations and reduce other complications by 80% to 90%, or even more. We think this is going to be *the* future of diabetes care." **EBDM**

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Diabetes Complicates Postsurgical Recovery, but Study Suggests Method to Identify Those at Risk

Surabhi Dangi-Garimella, PhD

For years, physicians have struggled to predict the postsurgical recovery time of their patients—a variable with unknown causes. Gauging the period of recovery gives patients a sense of how soon they may be up and about, returning to their normal lives and to work. A prolonged recovery time can have multiple consequences, including psychosocial ones for the patient and economic ones for society.

For persons with diabetes, recovery from surgery is particularly complicated. Research has shown that insulin resistance could result from surgery, and its intensity could define the recovery period. These patients also face a greater risk of infection and wounds that do not heal, leading to other health problems and higher hospital costs. Patients who suffer these complications risk being readmitted to the hospital, which brings on the added costs. The need to identify which patients face this risk has never been greater, as the Affordable Care Act (ACA) has brought new penalties for hospitals that see too many readmissions within 30 days of discharge.

Now, a new study from Stanford University has opened up the potential for predictive gene signatures and the development of a diagnostic test that could foretell clinical recovery. Such a test could have enormous value when surgical patients have diabetes, for it could help hospitals stratify and target patients for enhanced care to prevent readmission.

Traditional recovery parameters have included metrics such as length of hospital stay, while recent studies have focused on more patient-centered outcomes such as absence of symptoms, ability to perform regular activities, return to work, and quality of life. While there have been attempts to define the process of postoperative recovery, various stakeholders view the matter differently. One such definition attributes the following characteristics to recovery following surgery:

- an energy-requiring process
- a return to a state of normality and wholeness defined by comparative standards
- regaining control of physical, psychological, social, and habitual functions
- returning to preoperative levels of independence in activities of daily living
- regaining one's optimum level of well-being.[2]

The predictive test could have enormous value when surgical patients have diabetes—it could help hospitals stratify patients for enhanced care to prevent readmission.

Although the parameters for measuring recovery have evolved over the years, the available data are not sufficient for drawing predictions on the recovery period. Perioperative methods, such as enhanced recovery protocols, can accelerate recovery and reduce hospital stays,[3] but their impact on patient recovery following discharge remains unknown. In an attempt to solve this conundrum, researchers at Stanford University evaluated the molecular signature of patients undergoing surgery to predict patient recovery.[4]

Using mass spectrometry (MS) as a tool, the scientists measured precise changes in specific molecules of the immune system in patients who had undergone major surgery, including phosphorylation changes in signaling proteins. Whole-blood samples were collected from patients who had undergone hip surgery (primary hip arthoplasty). The samples, collected 1 hour before surgery and at predetermined times after surgery (1 hour, 24 hours, 72 hours, and 6 weeks), were stained with antibodies for cell surface proteins and phosphoepitopes of intracellular proteins, and analyzed by MS.

Researchers discovered that the activi-

ty of a fraction of the immune cells within the first 24 hours following surgery could be a predictive signature of how quickly a patient would recover from surgery-induced pain and fatigue. Simultaneous monitoring of subsets of immune cells provided a global view of immune alterations following surgery in innate and adaptive responses. Additionally, fatigue, pain, and functional impairment of the hip were assessed using 2 different scales: the Surgical Recovery Scale and the Western Ontario and McMaster Universities Arthritis Index.[4]

Analysis of the results corroborated previous findings: innate immune cells expanded soon after surgery, while the number of cells associated with the adaptive response shrank. As expected, signaling pathways were activated quite early in the process, and the responses were parallel to adaptive and immune cell responses. A feature of the current study was the evaluation of specific subsets of cells within the immune system, which helped identify and analyze responses that were likely missed in the global immune analysis conducted in earlier investigations.[4] When the results of the pain measurements were correlated with the molecular responses, researchers found a 40% to 60% variability in patient recovery rates.

The authors acknowledge that the study population suffered minimal comorbidities and that these patients underwent only 1 type of surgical procedure. Consequently, a likelihood of variation in immune response exists, based on the type of surgical procedure and the influence of comorbidities such as diabetes.

Surgical recovery can be complicated by comorbidities such as diabetes.

Diabetes Can Complicate Surgical Recovery, Extend Hospital Stays, and Incur Additional Costs

Because insulin resistance increases during surgery, a person who already has elevated blood glucose can experience problems when non insulin-sensitive cells rapidly absorb glucose. This could result in infections and cardiovascular complications, while a reduced glucose uptake in muscle could reduce muscle function and impair mobility.[5]

Diabetes-associated peripheral arterial disease can reduce blood flow to the surgical area, resulting in delayed recovery. Additionally, in patients who have poor control of their blood sugar levels, surgical wounds stand a higher chance of being infected, further delaying recovery. Taken together, surgical stress boosts the blood sugar levels in the body, which can develop into diabetic ketoacidosis and complicate the process even further.[6]

Those with type 1 diabetes mellitus (T1DM), the so-called juvenile or insulin-dependent form of the disease, appear to be at higher risk of surgical complications than those with type 2 diabetes mellitus (T2DM). A study conducted at the Duke University Medical Center evaluated surgical recovery and perioperative complications in patients who had undergone orthopedic procedures for joint replacement between 1988 and 2003. The analysis compared patients with T1DM with those suffering from T2DM, and found that T1DM patients had significantly longer hospital stays, and increased incidence of myocardial infection, pneumonia, urinary tract infection, postoperative hemorrhage, wound infection, and death, resulting in a significant uptick in the cost of care.[7]

Research presented at the 21st annual meeting of the American Association of Clinical Endocrinologists compared the length of stay following elective surgery in patients with diabetes and those without, and analyzed the influence of comorbidities and perioperative complications on healthcare costs. Using data from the Healthcare Cost and Utilization Project, the researchers found that patients with diabetes had a higher number of chronic conditions and comorbidities when admitted for surgery, compared with those without (7.6 vs 3.6 diagnoses). Additionally, diabetes nearly doubled the patient stay in hospitals: 9.08 days for those with diabetes versus 4.76 days for those without; the associated costs per patient were $19,547 versus $15,873.[8]

The study results point to increased complications in patients with diabetes undergoing surgery, resulting in longer hospital stays and, thereby, higher costs.[8] The longer stays are a drain on hospital revenue, so greater attention to maintaining the glycemic levels of these patients could have a tremendous impact on patient outcomes as well as healthcare costs.

CMS Challenges Hospital Vigilance

Complicated recoveries translate into higher readmission rates for surgical patients with diabetes. Findings ways to trim the length of hospital stays and prevent readmissions could lead to significant cost savings. The Healthcare Cost and Utilization Project, a federal-state-industry partnership, identified diabetes, mood disorders, and schizophrenia as conditions with the highest number of 30-day all-cause hospital readmissions for Medicaid. Complications associated with diabetes cost Medicaid $251 million in readmissions in 2011, accounting for 3.3% of the total cost of Medicaid readmissions.[9]

Both T1DM and T2DM were identified as risk factors for readmission in patients undergoing lumbar fusion surgery. While T2DM patients had longer hospital stays, T1DM patients had several complications post surgery, including sepsis, ventilator-associated respiration, wound-related infection, urinary tract infection, and pneumonia. These resulted in more extended hospital stays and readmissions within 30 days.[10] Medicare patients receiving a kidney transplant had a 29% increased incidence of 30-day readmissions in women with diabetes and a 12% increase in men with diabetes.[11]

With this kind of evidence, Medicare, through provisions of the ACA, established the Hospital Readmissions Reduction Program (effective October 2012), which mandates reduced reimbursement to hospitals participating in the inpatient prospective payment systems that have higher readmissions.[12] CMS hopes that these penalties will prod hospitals to take steps to better monitor patients at high risk of readmission, including those with diabetes. **EBDM**

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Nova StatStrip Glucose Hospital Meter System Approved for Use in Critical Care Patients

V. Silverstein

The FDA approved the Nova StatStrip Glucose Hospital Meter System for use among all hospitalized patients on September 24, 2014.[1] Nova StatStrip's system was first approved for such use by the FDA in 2006 to help monitor the effectiveness of a diabetes control program. The recent approval extends the use of this continuous glucose monitoring system in all capacities, including monitoring critically ill patients.

Multiple studies have shown that Nova StatStrip, which is indicated for hospitalized patients on complex medication regimens, accurately reports blood glucose levels when healthcare providers test patients with a wide array of medical conditions, including cardiopulmonary disease, endocrine disorders, malignancies, obstetric or gynecologic issues, renal disease, surgery, and trauma. Moreover, this device can use arterial or venous whole blood obtained from hospitalized patients of all ages, including neonates, children, and adults.

Glucometers (or blood glucose meters) are handheld instruments that allow healthcare workers to test blood glucose levels at the bedside. A single drop of blood pricked from the patient's finger is applied to a plastic strip, which is then inserted into the glucometer. Glucose in the blood reacts with an enzyme on the test strip, and the chemical reaction creates an electrical current, which is measured and displayed as a surrogate for the blood glucose level. The Nova StatStrip functions by using a modified glucose-oxidase-based amperometric test.[2] This device also corrects for interference and hematocrit levels. Other commonly used glucometers include the Accu-Chek Performa, Countour TS, OneTouch Ultra2, and the Optium Xceed. These glucometers vary in their level of accuracy, occurrences of error messages, and influence by hematocrit levels.[3]

In outpatient settings, people with type 1 (T1DM) or type 2 diabetes mellitus (T2DM) monitor their blood glucose levels using a glucometer. While individuals with T1DM, an autoimmune disease that interferes with insulin production, monitor their blood glucose levels to determine their insulin dose, those with T2DM, a disease of insulin resistance, usually require closer monitoring when they are sick, exhausted, or adjusting new medication regimens. Type 1 and type 2 diabetics require similar monitoring while hospitalized with injuries or illnesses.

Blood Glucose Monitoring in Hospitals

Diabetics are not the only patients who require close monitoring of blood glucose levels. The FDA's approval of the Nova StatStrip System for use in all hospitalized patients is relevant because so many hospitalized patients, including non diabetic patients, require blood glucose level monitoring to maintain euglycemia. Hospitalized patients are susceptible to hypo- and hyperglycemia. For example, neonatal and pediatric patients are at a particularly high risk of sustaining brain damage if they become hypoglycemic; cardiac surgery patients are at an increased risk of wound infection following prolonged hyperglycemia; and uncontrolled glucose levels in intensive care unit patients are associated with impending sepsis.

Insulin and glucose levels vary dramatically in response to infection, inflammation, injury, and other pathologies requiring hospitalization. Sustained hyperglycemia, defined as fasting glucose levels consistently above 130 mg/dL, leads to problems that mirror uncontrolled diabetes: patients experience increased inflammation, risk of infection, changes in coagulation, macrovascular and microvascular disease, and aberrations in lipid levels.[4] Hypoglycemia, described as blood glucose levels below 60 mg/dL, may prove more dangerous for patients in the short term. Low blood glucose levels may lead to loss of consciousness, falls, seizures, cardiac arrhythmias, coma, and even death.

As a result of the health problems that have led to their hospitalization, patients are already highly vulnerable to endogenous fluctuations in glucose levels. In addition, once hospitalized, dietary changes and new medications can greatly influence their glucose levels. For example, patients almost always fast prior to surgery or certain procedures, and they may not eat normally for several days afterward. Consequently, hospitalized patients who are fasting preoperatively or have anorexia postoperatively are at an increased risk of hypoglycemia and hyperglycemia.

Within the hospitalized patient population, critically ill patients are particularly vulnerable to changes in blood glucose levels and often suffer from stress-induced hyperglycemia that is prolonged by long-term inflammation and subsequent infections. Medications, including steroids, can also increase blood glucose levels, while glucose-containing intravenous fluids further worsen hyperglycemia.

Healthcare providers often worry much more about the immediate risks associated with low blood glucose levels. Studies report that the range of hospital-associated hypoglycemia is 1.2% to 20%.[5] Factors that can lead to hypoglycemia in hospitalized patients include underlying illness, nothing-by-mouth status, infrequent glucose monitoring, transitions of care, and complex medication regimens.[6,7] Furthermore, critically ill patients are frequently intubated and/or sedated, and they cannot express subjective symptoms of hypoglycemia, increasing the possibility of a missed diagnosis.

Critically ill patients are often fed intravenously or by tube feedings. The amount of glucose in the intravenous fluids, total parenteral nutrition, or tube feeds must be recalibrated based on the influence of altered gut absorption, interference with other medications, and fluid status. As adjustments are made to the nutritional support, healthcare providers must carefully readjust the insulin and glucose they administer based on the patients' blood glucose levels.

Many critically ill patients cannot swallow oral antidiabetic agents because of the severity of their disease, renal dysfunction, fasting, or intubation. If they have dramatic swings in their blood glucose levels, they require sliding scale insulin or continuous intravenous insulin and frequent monitoring. Under these circumstances, healthcare providers may need to check the blood glucose levels of critically ill patients as often as hourly or every few hours and adjust the insulin dose to maintain euglycemia. Optimally, testing at the bedside would allow for better care than sending repeated blood draws to the laboratory for glucose analysis. But before the FDA approved the Nova StatStrip in September, no bedside glucometer had been approved for use with critically ill patients.

Traditionally, blood samples from critically ill patients have been sent to the hospital laboratory for analysis. Despite delivering the most accurate measure of blood glucose levels, it is not always safe or feasible to send all blood samples to the hospital laboratory.[3] If a patient is unconscious or has altered mental status due to hypoglycemia, diagnosing hypoglycemia immediately becomes vital for the medical team, and they cannot wait for the blood sample to reach the lab. Therefore, portable glucose meters may be the safer option. Similarly, if an unstable patient is being followed with hourly blood glucose evaluation, the turnaround time for the lab to evaluate a blood sample is too long to be useful, and the amount of blood required for repeated blood draws may be too high and lead to iatrogenic anemia. As a result of these factors, healthcare providers may find that portable glucose meters, such as the Nova StatStrip, are a better choice.

FDA's approval for Nova StatStrip for use in all hospitalized patients, including non-diabetic and critically ill patients, is relevant because so many require blood glucose monitoring.

The Nova StatStrip has been approved for use in neonatal and pediatric patients, as well as adult patients. Hypoglycemia in neonates can cause brain damage, and accurate diagnosis of low blood glucose levels in newborns becomes imperative.[8] Studies show that the StatStrip has good clinical accuracy for measuring point-of-care glucose levels in neonatal patients, and the glucometer does not encounter interference from hematocrit, bilirubin, or maltose levels.[9,10] The device also works well in assessing hypoglycemia and hyperglycemia in older children. Exhibiting a good correlation with actual blood glucose levels, StatStrip works quickly even with a small volume of blood.[11]

The device, now approved in critically

If an unstable patient is being followed with hourly blood glucose evaluation, the turnaround time for the lab to evaluate a blood sample is too long to be useful.

ill patients, also meets CLSI POCT 12-A3 accuracy criteria and has decreased glucose meter bias with fewer insulin dosing discrepancies.[12] The Nova StatStrip Glucose Meter has been cleared with a "waived" test status for all settings under the Clinical Laboratory Improvement Amendments, and it does not have to meet requirements for high complexity testing. Per the FDA, the device is easy to use and has low risk for false results. Therefore, healthcare professionals, including nurses and technicians, can perform the test at the patient's bedside instead of having to send blood to the hospital laboratory for analysis.[13] Additional studies suggest that the StatStrip is also a good option for glucose testing in tertiary care settings.[14]

In the FDA's press announcement, Alberto Gutierrez, director of the Office of In Vitro Diagnostics and Radiological Devices at the FDA's Center for Devices and Radiological Health, is quoted as saying, "This device provides an important public health resource for critically ill hospitalized patients, who often have conditions or are taking medications that can cause incorrect blood glucose reading. It is important for manufacturers of glucose meters used in hospitals to design and test their devices for use in all hospitalized patients."[1]

The Nova StatStrip Glucose Hospital Meter System is manufactured by the Nova Biomedical Corporation located in Waltham, Massachusetts. **EBDM**

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Research Report

Environmental Factors, Not Just Genes, Cause Type 1 Disease

Surabhi Dangi-Garimella, PhD

For a long time, type 1 diabetes mellitus (T1DM) was considered a genetic autoimmune disease. Yet, correlations have been found between T1DM and environmental triggers such as viruses, with the seasonal onset within populations being the cue. But so far, the evidence has been largely circumstantial. Rotavirus, rubella, and mumps infection have been studied and disregarded[1]; studies in a Finnish population disproved the rotavirus connection,[2] while successful vaccination campaigns that largely eliminated the 2 viruses could not curb T1DM.[3,4] However, there is validity to claims of an association between enteroviral infections and acceleration of islet autoimmunity, as was shown in a recent report from Taiwan.

A national population-based retrospective study compared the incidence of T1DM in children diagnosed with the enterovirus (EV) with that in age- and gender-matched children without EV infection in Taiwan. The study found increased susceptibility in the EV-infected children.[5] The study utilized claims data from Taiwan's National Health Insurance program between the years 2000 and 2008, with a study population that included children 18 years and younger.

With an adjusted hazard ratio of 1.48, the incidence rate was 5.73 for the infected children compared with 3.89 in the uninfected cohort, per 100,000 person-years. Additionally, when the authors examined the influence of atopic disease status in the children as a variable that could influence susceptibility to T1DM, they found that children in the EV group had significantly higher rates of atopic dermatitis, allergic rhinitis, and bronchial asthma. Age was another variable that determined incidence, with younger children (5 to 7 years old) and those over 10 years of age showing increased incidence of T1DM independent of their EV status. Based on previous studies, the authors concluded that increased incidence in the younger age group may correspond with the children starting school, while the second spike in older children may correspond with hormonal upheaval as the children entered puberty.[5]

The authors argued that while genetics are a factor, genes alone cannot explain the rapid rise in the number of cases of T1DM across ethnicities and geographic locations. The DiaMond Project, for instance, evaluated T1DM incidence between 1990 and 1999, and identified a steep rise among European children, especially in Sardinia, Sweden, Finland, Norway, Portugal, and the United Kingdom, as well as in Canada and New Zealand. Quite surprisingly, incidence increased with age, with 10-to-14-year-olds being the most susceptible.[6] This and similar studies provide evidence for environmental factors, such as chemical exposure and infections, being possible triggers of disease.

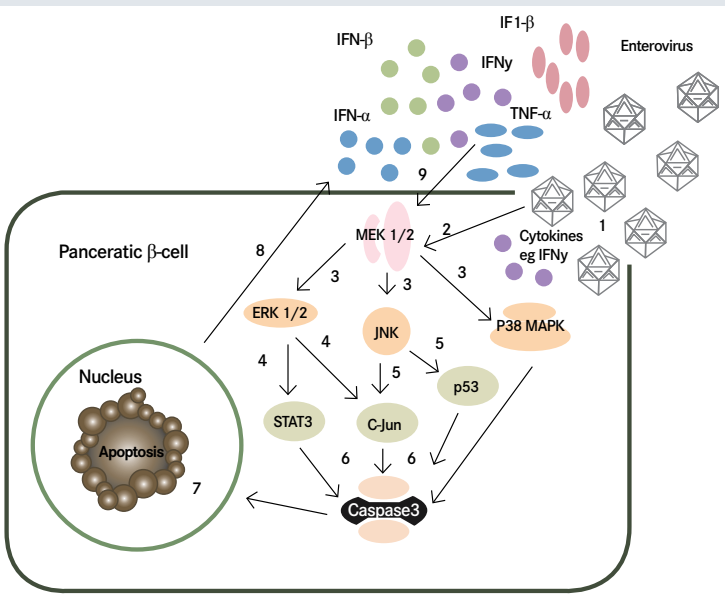
Enteroviruses Detected in the Pancreas in T1DM

Better technology has improved the sensitivity of tests for viral detection. In 2009, a paper published in *Diabetologia* described the results of reexamining paraffin-embedded samples from 72 recent-onset T1DM patients and 161 controls. In addition to several immune response proteins that are produced in the pancreatic islets following a viral infection (PKR, class I MHC), expression of the EV capsid protein VP1 was examined.[7]

Multiple VP1-immunopositive cells were identified in multiple islets of more than 60% of the 72 samples of young, recent-onset T1DM patients, compared with only 6% of the 50 neonatal and pediatric normal controls. Of note, the VP1 expression was restricted to insulin-containing β cells, implicating the virus in cellular destruction. The authors conclude that genetic predisposition to T1DM, coupled with an EV infection of the β cells, can precipitate autoimmunity in young children.[7]

Despite this and similar studies, pinpointing a specific viral strain has proved challenging. Why would that be? Clinical disease onset, measured as the development of clinical hyperglycemia, likely happens months or years after the

Figure. Enterovirus Triggers β-cell Apoptosis



Enteroviral infection of the islet cells in the pancreas activates a cascading signaling pathway, including the MAPK proteins (ERK, JNK, and p38), followed by activation of STAT3, c-Jun, and p53. The activated proteins then converge onto caspase 3, resulting in cellular apoptosis. The signal is further amplified by the recruitment of cellular cytokines, namely IFN (α, β, γ), IL1-β, and TNF-α.

ERK indicates extracellular signal-regulated kinase; IFN, interferon; IL, interleukin; JNK, c-jun N-terminal kinase; MEK, mitogen-activated protein kinase kinase; STAT3, signal transducer and activator of transcription; TNF, tumor necrosis factor.

Source: http://microbiology.publish.csiro.au/paper/MA13051.htm.

initial infection(s) that lead to the autoimmune loss of the islets. So when patient samples are analyzed, traces of the trigger may be long gone. Additionally, even if an individual is positive for the virus, confirming whether the virus is diabetogenic can be difficult.

So can immunization against EV or other suspect viruses help curb the current worldwide epidemic of T1DM? A global consortium of scientists—from research institutes to vaccine companies—says perhaps, and are working toward developing an EV vaccine to prevent the occurrence of T1DM. This effort would identify the diabetogenic serotype of the virus in different populations. Prototype vaccines are also being evaluated in mouse models.[8] **EBDM**

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CDC Data Show How Managed Care Missed Opportunities With New Diabetes Cases

Mary K. Caffrey

Helping patients with diabetes mellitus learn to maintain glycemic control is important, both for improving their long-term health and for controlling costs. So why did so few newly diagnosed patients with private insurance enroll in diabetes self-management training?

CDC findings released November 20, 2014, for the years 2011 to 2012 are a cause for concern, both for patient health and for bottom lines. Diabetes care is a key focal point for accountable care organizations (ACOs), which are subject to new Medicare reimbursement formulas under the Affordable Care Act (ACA).

The study, included in the CDC's *Mortality and Morbidity Weekly Report*, examined records of 95,555 newly diagnosed persons with diabetes. Of these, 25.6% were not prescribed any antiglycemic medications, and 6.8% were prescribed insulin, with or without oral medication. During the study period of 2011 to 2012, 6.8% of the newly diagnosed patients took part in diabetes self-management training within 12 months of diagnosis.[1]

Using Marketscan data, CDC researchers found that participation rates were slightly higher among older patients, aged 45 to 64 years, compared with younger adults, aged 18 to 44 years (7.2% compared with 5.9%), and among those who received a prescription for insulin compared with those who received a prescription for oral agents only (14.2% compared with 5.1%). Those in metropolitan areas were more likely to participate in training compared with those outside such areas (7.1% compared with 5.5%).[1]

In discussing the findings, researchers expressed concern that among all subgroups studied, the highest level of diabetes self-management training was only 15%, even though this study included patients with private insurance—in theory, a group for whom lack of insurance coverage should not be a barrier to participation. The study identified several potential barriers:

- lack of physician referrals
- personal perceptions about diabetes, including avoidance behaviors
- lack of awareness that diabetes self-management training exists.[1]

Researchers warned that failure to participate in self-management training could reduce the likelihood that blood glucose remains well controlled, which could lead to higher treatment costs down the line.

It is noteworthy that much has changed since the study period. ACOs now keep track of patients with diabetes, and many have specific programs in place to help those newly diagnosed understand the importance of managing their disease and maintaining glycemic control. The "diabetes bundle" has become part of the 33 quality measures tied to Medicare reimbursement. An ACO that allows its physicians to fail to refer newly diagnosed patients for self-management training would risk lower quality care ratings the following year.[2]

In sessions of the ACO and Emerging Healthcare Delivery Coalition, an initiative of *The American Journal of Managed Care,* participants have shared new methods for helping patients manage their diabetes.[2] **EBDM**

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Night Shift and Diabetes
(continued from cover)

shifts fared much, much worse. A decade or two of rotating shift work was associated with a 40% increase in diabetes risk, and any more than 20 years was associated with a 60% greater risk.[1]

The newest research on the links between shift work and diabetes aggregated data from Hu's paper and 11 other international studies, in an effort to better quantify and to conduct analysis on various subgroups.


Martin Moore-Ede, MD, PhD

The meta-study, which was published this past summer in *Occupational & Environmental Medicine*, found that any amount of time spent doing shift work was associated with a 9% greater risk of diabetes (95% CI, 1.05-1.12; *P* = .014).

The study's major finding was that it identified a more significant correlation between shift work and diabetes in men than in women. Multivariate analysis suggested that men with any exposure to shift work were 37% more likely to develop diabetes than men who worked days (95% CI, 1.20-1.56).[2]

Moreover, rotating shifts appeared more hazardous than steady night work: the meta-study identified a 42% increase in diabetes risk due to rotating shifts, among both genders (95% CI, 1.19-1.69). And diabetes is only one of many health risks associated with working during odd hours.

Several studies have found significant associations between shift work and various forms of cancer. A much-cited paper from the *Journal of the National Cancer Institute*, for example, found that steady night work was associated with a 60% increase in the risk of breast cancer.[3]

An even greater body of evidence suggests that shift work increases the risk of cardiovascular disease. A large meta-study from 1999 concluded that shift workers faced a 40% greater risk of cardiovascular disease than daytime workers.[4]

Ulcers? Nearly quadruple the risk.[5] Metabolic syndrome? Up to a 5-fold increase.[6] Hypertension? 81% more common in African American female shift workers.[7] Depression? Probably.[8]

"Shift work fundamentally disrupts the body's efforts to rest and repair itself, so it's hardly surprising that it produces a wide range of negative biological effects in many people," Hu said.

"But the effects are not only biological. Shift work affects important behaviors. It causes people to eat worse, exercise less, and socialize with fewer people. All of those behaviors have biological effects of their own, and, again, they're all negative."

Yet even as the evidence of shift work's toll continues to grow, the number of people working nights may also be on the rise.

Some shift work, of course, is indisputably necessary. Police departments and hospitals must operate at night. The rationale for other shift work, however, is purely economic. A 3-shift operation generates 3 times the return on capital as a 1-shift operation. Truckers fight less traffic at night. Overseas clients expect suppliers to work on their hours.

Economics drives employee decisions as well. Shift work often provides a huge premium over available work, particularly for unskilled employees, or it may be a necessary stepping-stone to day work that's reserved for senior employees.

Unfortunately, according to many who study shift work, employers and employees often make bad economic decisions because they do not fully understand the true costs that odd hours impose on the body.

Research from Circadian, a Massachusetts-based company that helps employers optimize their off-hour operations, indicates that the total cost associated with shift work averages more than $10,000 per employee per year.[9]

That figure accounts for lower productivity, higher error rates, increased turnover, inflated absenteeism, and several other factors. Increased health spending alone accounts for a significant percentage of the total. Indeed, shift workers account for 10% of all Americans with health insurance but 17% of healthcare spending.[9]

Most operations with any significant number of shift workers bear that cost directly because they self-insure. Smaller companies that purchase coverage rarely pay an explicit premium for shift workers. However, high claims from shift workers in one year influence the next year's rates.

Employers, in other words, have a big financial incentive to mitigate the costs of shift work, but Circadian's research indicates that most of them take no systematic steps.

Many logical strategies for mitigating those dangers aren't even legal. For example, a company that saw the diabetes meta-study and tried to save employees from decades of chronic illness by assigning women and other low-risk candidates to shift work would risk lawsuits, union action, government intervention, and terrible publicity.

Considering that research and anecdotal experience both indicate that some people naturally tolerate shift work much better than others, such restrictions significantly limit the potential efficacy of harm-reduction efforts.

Still, they exist. So employers who want to minimize the economic and human toll of shift work must focus on self-help for the employees who land in the job.

At companies where most people work the usual day shift, logistical difficulties often minimize the benefit shift workers receive from general health initiatives. Nutrition classes that begin at noon are useless to them. The fitness trail in the woods behind the parking lot is no fun to walk at night. And the healthy options in the cafeteria do nothing for people who arrive after it has closed.

Still, companies have options.

Viridian Health Management, a Phoenix-based population health management company that helps many large companies maximize employee wellness, advises clients to inform shift workers about the associated risks and to remind them periodically.

"Many companies hesitate to tell workers about any job-related risks they're not legally obligated to disclose, which is self-defeating. You can't expect people to work hard to prevent serious health problems if they don't know they're at risk in the first place," Viridian's chief medical officer, Eric Dinenberg, MD, MPH, told *EBDM*.

"At the very least, employers with shift workers should communicate the facts, outline some basic strategies for coping, and stress the need for regular screening that can spot problems early. But given the stakes involved—once a person develops diabetes, healthcare costs double—employers should do much more," Dinenberg added.

Dinenberg believes that employers need to include screenings for health risk factors for diabetes and other chronic conditions that reach third-shift workers. He also urges all companies to offer all workers on all shifts regular opportunities to participate in a diabetes prevention program that conforms to CDC guidelines. Research has found that such programs reduce the risk of a pre-diabetic individual developing diabetes by more than 50%.[10] Better still, program costs are moderate. Groups meet once a week for 16 weeks and once a month for another 6 months. At each meeting, a lifestyle coach helps participants develop strategies for eating better, exercising more, and identifying emotions and situations that can get them off track.[11]

The facilitator doesn't have to be a costly healthcare professional. Research shows that diabetes prevention programs facilitated by lay educators without any clinical background are as effective as programs facilitated by clinically trained professionals.[12]

Motivation is important, however, and forward-thinking employers use incentives to encourage employee participation, Dinenberg said.

Given the size of the problem—86 million American adults now qualify as prediabetic[13]—nearly all employers have


According to new research, working the night shift can take a toll on one's health.

reason to consider such programs, but they're relatively rare among companies with large numbers of shift workers (and other companies as well), despite the economic incentives.


Frank Hu, MD, PhD

Wellness programs aimed at shift workers often pay for themselves (or even generate automatic profits) because many health insurers offer automatic discounts for workers who attend them. Looking forward, the financial incentives could grow larger still if workers' compensation insurers were to offer incentives to employers who get staff to complete these programs. Discounts on workers' compensation policies are not currently given, insurers told *EBDM*.

Sleepy shift workers have significantly more accidents on the job than people who work days,[14] and the health complications they help to cause make problems worse. Studies have shown that obesity and diabetes are both associated with more errors in the workplace. Effective wellness programs, therefore, would reduce workers' compensation claims as well as traditional health costs.

Employees, naturally, face some financial incentives of their own. More trips to the doctor and the drugstore translate into larger annual co-payments.

Employers cannot legally increase those incentives by making shift workers contribute more to their healthcare policies than comparable day workers or by increasing their co-pay rates. They can, on the other hand, provide some discounts to employees who reach certain health targets or complete wellness programs. (This is actually a bit of a legal gray area, and laws vary among the states, but employers are experimenting.[15])

Employers can also address the general effects of shift work directly, rather than address the specific conditions that odd hours can trigger.

"There are steps that can produce significant benefits without any conscious behavioral changes from anyone," Circadian chairman and chief executive officer Martin Moore-Ede, MD, PhD, told *EBDM*. "Some shift schedules are dramatically better for workers than others, and changes to the office environment, particularly the lighting, can also help workers adapt to the unusual hours."

A comprehensive strategy that combines environmental improvements with worker training can generally reduce the extra costs associated with shift work by about 50%—and greatly improve the health and happiness of workers.

"Workers tend to be skeptical when they start the training, but once they begin trying the strategies and getting better rest, they become very enthusiastic," Moore-Ede said. "That's not to say that any combination of strategies can fully control our internal clocks or eliminate the practical difficulties of working when everyone else sleeps. They can, however, produce dramatic benefits in terms of employee health, employee happiness, and the bottom line." **EBDM**

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Technology in Diabetes Apps
(continued from cover)

make healthy choices.[4] The evidence, to date, is mixed.

On the one hand, the app stores for Google and Apple customers offer about 1100 programs designed to help patients with diabetes manage their health or otherwise cope with their disease. On the other hand, surveys suggest that only about 1.2% of all Americans with diabetes actually use any of those apps regularly.[5]

"Most of the apps that are out there right now do only one thing, and it's typically not even a particularly useful thing," said David Kerr, director of research and innovation at the William Sansum Diabetes Center in California. "The single most common thing we see right now are apps that ask you to laboriously type in lots of data before then presenting those very data back to you in the form of a pie chart or a bar chart. Apps need to be designed with 'health clarity' in mind. They need to be easy to understand and use. They also need to take data and put them into a personal context in order to guide the user to change behavior."

Kerr blames a number of factors for the "shambolic" state of the health-app industry, factors that range from the general lack of design input from individuals with diabetes, to the inherent difficulty of producing something sophisticated enough to be useful, to the understandable concerns about regulation from the FDA, to the financial risk of making a world-beating application affordable to consumers.

These are all serious concerns for app makers, who tend to succeed by quickly churning out programs and then giving them away or selling them cheap. Investing millions of dollars up front on a single app and then hoping that it proves valuable enough to recoup that cash is a risky proposition. It's riskier still to design something that might fall under FDA scrutiny and thus may have to prove itself safe and effective before it can go on sale.


Kyle J. Rose

The FDA only regulates a tiny fraction of health apps—theoretically just those that work with regulated medical devices and those that "transform a mobile platform into a regulated medical device"[6]—but many app makers want to steer far from oversight by sticking with simple tasks, like converting data to bar charts.

All that said, a few companies have taken the plunge and subjected themselves to FDA regulation by developing sophisticated apps that have proved their ability to make diabetics healthier.[7]

A company called mySugr offers a diabetes management app that, while still requiring data entry and producing pretty graphs, can also analyze what users tell it about food, blood readings, and other factors to help identify how medication affects users and what patterns their behaviors follow.[8] The company's software, which was originally aimed primarily at

people with type 1 diabetes mellitus, also tries to motivate users with frequent challenges and by personifying their disease as a visible "monster" that can be tamed by judicious behavior.

"This is a product made by people with diabetes, for people with diabetes. Our founders had tried all the other apps before they starting building this. They knew what diabetics wanted and where software typically tended to fall short and often still does today," said Kyle J. Rose, mySugr's business development director, in a conversation with *Evidence-Based Diabetes Management*.

"Programs like this need significant information to provide significant feedback, so the program tries to make input as easy as possible with passive data collection, like geo-tagging, for example, and it tries to make the process fun by turning it into a game. You get points every time you enter information, and those points help you tame your monster."

The mySugr app called "Companion" offers some pretty sophisticated services. It can, for example, "remember" venues where users have reported experiencing health problems (say, hyperglycemia at an ice cream shop) and thus inspire the user to choose a different treat, choose a different dose of medication, or perhaps even avoid the location altogether. A simple version of the app for either iOS or Android is available for free, but the "pro" version costs $19.99.

Another app the FDA has approved, this one specifically for managing type 2 diabetes mellitus (T2DM), costs considerably more. WellDoc's BlueStar system retails for roughly $100 a month, but it's prescribed by a doctor and reimbursed by insurance, just like other prescription-only medical health devices. The software tool, which reduced glycated hemoglobin levels by 2 points in randomized controlled trials, utilizes the information provided by each user to learn about their body and make customized, clinically validated recommendations.[9]

BlueStar, like many of the most sophisticated medical "apps," isn't really an app at all. Only a tiny portion of it resides on user phones and computers. Most of the product resides in very large servers that can do complex analysis, and other portions reside in the electronic health record (EHR) systems that physicians use. Once a doctor prescribes BlueStar, the patient's EHR, treatment plan, and physician's orders are loaded into the program to custom-tailor the algorithms for each patient. Then, in most cases, a WellDoc trainer visits the new patient to help install BlueStar on smartphones, tablets, and/or computers and then explain the basics of using the system. If questions arise afterward, patients (and doctors) can call for live help.

While BlueStar allows patients to enter endless amounts of information about themselves, it also works for patients who only provide data a few times a week. "Most people simply won't put in several hours of work per week on this stuff, but fortunately, they don't have to," Chris Bergstrom, chief strategy and commercial officer at WellDoc, told *EBDM*. "BlueStar will give you valuable feedback every time you engage it, whether it's twice a week or 6 times a day. You'll get more out if you put more in, but everyone gets actionable information, in the right form, at the right time."

Wearable devices track a person's vitals and relay them to the provider through a smart device.

Fortunately, entering information into programs like BlueStar and mySugr Companion may soon become much easier, and Dexcom's recent announcement illustrates why. Wireless communications technology has improved to the point where many medical device makers have decided to make products that can automatically share information with tablets, smartphones, and other devices. The process is under way at every type of company, making every type of device, to measure every type of variable: weight, body fat, blood pressure, heart rate, cholesterol, blood alcohol, blood sugar, exercise duration, calorie expenditure, and countless others.[10]

Improved hardware has certainly helped drive the trend. The components required for Wi-Fi, Bluetooth, and cellular communications have all gotten better, cheaper, and smaller over the past few years. Better software, however, is playing an even bigger role.

Until recently, many efforts to sync any 2 products from any 2 companies required custom software. Some companies did form partnerships. mySugr, for example, has teamed with Sanofi on software that lets its companion app upload information directly from iBGStar glucose meters.[11] But the sheer amount of effort limited the number of products that communicated. That changed this summer when Apple released HealthKit, a program that creates formatting standards for all kinds of health data and acts as a repository for properly formatted data—extracting it from any device that provides it and transmitting it to any program that accepts it (under the control of the user, of course).

Dexcom's new Share device, a cradle that holds the handset from its G4 Platinum continuous glucose monitoring system, uses Bluetooth to send information from the cradle to an iPhone or iPod Touch, which sends the information on to the Cloud. From there, up to 5 "followers" can look at the data and set up the system to send them notifications. The Share system will use HealthKit to make the patient's glucose data available, under the patient's control, to other apps on the patient's iPhone. The same functionality will be built directly into Dexcom's fifth-generation (G5) continuous monitor, which will still offer a Dexcom handset to patients who want one, but will work directly with Apple, Android, and possibly other mobile systems for other users.

Jorge Valdes

"This technology offers a lot of significant advantages. Users have one less screen to carry around. They can monitor glucose privately on a standard phone rather than an unusual device that people ask about. Their loved ones can get automatic alerts about potential problems. Their doctors can get information easier. And, of course, patients can transfer information from their monitor to any compatible software they use," Jorge Valdes, Dexcom's chief technical officer, told *EBDM*.

Dexcom is also working with researchers at Stanford University on a related trial, one that explores the effect of taking information from the company's products and transferring it via HealthKit directly into the most popular EHR systems.

"We've always believed that the information from our devices could produce value, but have chosen to spend our limited resources improving our actual devices to produce customized software for every potential partner or application," Valdes said. "Having standards that work with a lot of products makes it a manageable task and allows the information from our devices to flow pretty much wherever it will do the most good."

Valdes isn't the only one who expects standards, like the ones from HealthKit, to precipitate dramatic new uses for underused medical information.

There are, however, obstacles that may hinder such efforts. First, technology may prove unable to automate the collection of some very important types of data, like blood sugar and food nutrition.

Apple, to use a big example, generated much excitement with several moves that suggested it might include a monitor that measured blood sugar through the skin on its new watch.[12] Unfortunately, barring any last-minute announcements, the first generation Apple

Watch won't have such a monitor, presumably because the technology isn't ready for prime time.[13]

Food is almost as big a sticking point. It's easy to track nutrition information for home-cooked meals and to scan bar codes on packaged foods and even to use guides for chain-restaurant meals. But although researchers are looking for solutions,[14] there's no way to snap a picture of a meal at a friend's house or the little restaurant on the corner and get reliable information about carbohydrates and sugar.

Second, even if such things existed, they might do little good for most diabetics, who are disproportionately old, disproportionately poor, disproportionately afflicted with mental health issues, and, thus, disproportionately unlikely to have an app-capable cell phone, let alone a collection of cutting-edge devices.[15,16]

Third, lack of information isn't really the big problem for most people with chronic ailments. Nearly everyone with T2DM realizes they could minimize their health problems by eating a low-carb diet, exercising, and maintaining a healthy weight.

"I believe that information technology can produce significant benefits to human health, but I also believe the marketing hype has created unrealistic expectations," said Kerr, the research director at Sansum Diabetes Center. "Linking a scale and a treadmill to an iPhone and using the data to make a bunch of those bar charts won't transform lives. But the potential is there. Providing clear information, when it's most important, and providing it in a way that maximizes the motivation for action, can make people healthier. It's just going to take us longer than a lot of people expect to put it all together, and the answer will hinge more on the psychology of motivating people than on simply providing easy information." **EBDM**

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CVS: Care Management
(continued from cover)

disease, kidney disease, vascular disease, amputations, and blindness.

Health systems, Accountable Care Organizations, healthcare plans, and healthcare providers are actively seeking cost-effective ways to mitigate the rise of chronic diseases. As the payment spectrum continues to evolve and move from volume- to value-based models, providers gain more influence over patient care management and decisions. Because chronic conditions such as diabetes can affect so many other aspects of health, a multitude of providers are involved in administering care. In the interest of coordination, a team-based approach is most effective in managing the inherent complexity of the disease. CVS Health is actively engaging with health systems across the country to help coordinate this comprehensive care for patients, offering chronic disease monitoring as well as clinical support, medication counseling, and wellness programs.

CVS Health has now engaged with more than 40 major health systems throughout the country to help support population health management and to provide low-cost, high-quality care alternatives. While providers are accountable for patient health outcomes, they do not have full visibility into their patients' behavior outside their office or the hospital. These health-system collaborations aim to equip primary care providers (PCPs) with key information collected through CVS pharmacists that will assist them in making sound clinical decisions, such as reports on their patient population's medication adherence. Through this team approach to patient care, CVS Health is supporting providers' care plans, communicating critical patient care information, and enhancing connectivity to manage health in a more coordinated, affordable, and efficient way.

Patrick Gilligan,
Senior Vice President, Health System Alliances, CVS Health

Poor adherence to medications and reduced access to primary care are 2 main drivers responsible for the increased incidence of complications accompanying manageable chronic diseases such as diabetes. CVS Health is well positioned to help address both of these causes—in collaboration with its affiliates—through various adherence interventions and low-cost, high-quality health services offered by MinuteClinic, which complement primary care.

Three key stakeholders are responsible for managing a patient's medication adherence: the provider, the pharmacist, and the patient. Adherence to a medication regimen—critical for patients suffering from a chronic disease—means taking the same medication every day. Research shows, however, that many patients, even many of those with chronic conditions, do not take all the prescriptions essential to their medication regimen on a consistent basis.[3] Only 50% of patients adhere to medications as prescribed by physicians, and less than 40% of patients remain adherent 2 years after the initiation of a medication.[4] While predicting nonadherence is difficult, owing to its many associated causes, pharmacists are best equipped to quickly identify patients who are not taking a medication and could therefore be at risk. CVS Health has developed algorithms and processes to identify and connect with affiliates' patients who are nonadherent or need additional counseling regarding their medications. Electronic Medical Record (EMR) integration facilitates communication and data sharing between providers and CVS Health without negatively impacting the work flow in the physician's office.

CVS Health performs a comprehensive series of adherence interventions for its customers, including reminders to pick up, refill, and continue taking medications. Data regarding the number and type of interventions performed is then sent to providers in aggregate and condition-specific reports. Furthermore, CVS Health can identify patients who are deviating from their prescribed regimen and alert the provider. If a person with diabetes only fills and picks up 2 of the 3 medications prescribed, CVS Health

will call to remind the patient to pick up the third medication and report the nonadherence directly to their provider's EMR. These interventions and messages enable providers to access and review actionable information regarding their patients' current adherence at the point of care.

Understanding the medications prescribed following a hospital transition can be difficult, particularly for patients with chronic diseases. A patient with diabetes, already on multiple medications for their condition before they go to the hospital for a surgery, may be sent home from the hospital with additional prescriptions. This patient may face obstacles both in obtaining this new medication and in understanding how it could impact their current medications. To ease the process, CVS/pharmacy can deliver new medications to a health system affiliate's patient at their hospital bedside and offer education regarding the medication prior to discharge. A CVS pharmacist can follow up with the patient post discharge to ensure that they understand their medications and to encourage continuing care with their PCP. In addition, a pharmacist can review and reconcile the patient's list of medications, ensuring that there are no safety concerns regarding drug interactions with existing medications. If the patient is identified as having an increased risk for complications or readmission, the healthcare system and CVS Health can coordinate an in-home pharmacist visit for the patient. All this information will then be reported back to the patient's provider through the integrated EMR.

Patients with chronic diseases often need ongoing support to understand the medications they routinely take, and commonly rely on their local pharmacist. CVS pharmacists have the opportunity to connect more frequently with patients than other providers because patients visit the pharmacy more often than other healthcare settings. To optimize these touch points, CVS Health offers one-on-one pharmacist counseling for patients with common, but costly, chronic conditions. Studies have shown that one-on-one counseling can significantly improve medication adherence for this population by delivering proactive, patient-specific interventions. Greater patient engagement and active pharmacy care can improve chronic disease management, and in turn, patients' overall health.

A Retail Medical Clinic Adds Value to Patient Care

Often, patients with chronic conditions need routine screenings or tests to monitor their condition. CVS Health collaborates with affiliates to identify patients from their panel who would benefit from a reminder on an upcoming screening or test. A PCP identifies a patient with diabetes who is due for a foot exam or glycated hemoglobin test, and the CVS pharmacist delivers the reminder message to the patient when they come to the pharmacy to pick up a prescription. CVS Health's retail medical clinic, MinuteClinic, is available to an affiliate's patients for many of these services, simplifying the process for the patient. If the patient chooses to be seen at a MinuteClinic, the nurse practitioner will conduct the exam and report the results directly to the patient's provider. For the patient, this simple integrated approach provides value through coordinated, lower-cost care; easy access to health maintenance testing; and coaching and coordination with their provider. For the provider, value is created through improved adherence, reduced hospital admissions, a coordinated team of pharmacist and nurse practitioner collaborators, and financial benefits from risk contract savings and quality.

CVS Health performs a comprehensive series of adherence interventions for its customers, including reminders to pick up, refill, and continue taking medications. Data regarding the number and type of interventions performed is then sent to providers.

Beyond improving pharmacy care and medication adherence, CVS Health is working to address the impact of other healthcare issues on patient outcomes, including the profound shortage of PCPs in the United States. This shortage is evident in the fact that 50% of patients seen at MinuteClinic locations report that they do not have a PCP. MinuteClinic provides patients access to convenient, quality, low-cost healthcare that is complementary to and supportive of the provider and patient care medical home. CVS Health currently operates more than 940 Joint Commission accredited clinics in 30 states, and plans to expand to 1500 clinics across 35 states by 2017, at which time 60% of the American population will be within 10 miles of a clinic. In addition to addressing the shortage of PCPs, MinuteClinic can help support the increased focus on wellness and prevention as part of the overall healthcare solution to managing chronic conditions such as diabetes. As an extension of the healthcare team, MinuteClinic nurse practitioners and physician assistants offer joint clinical programs that target comorbidities, including hypertension and weight loss, as well as tobacco cessation programs. For patients without a PCP, a list of PCPs accepting new patients is provided at the time of the visit in an effort to connect the patient to a medical home for long-term follow-up of chronic conditions and for other medical needs.

To further underscore its commitment to treating patients with chronic disease, CVS/pharmacy has removed cigarettes and all tobacco products from its stores nationwide.[5] Tobacco products often cause or exacerbate chronic diseases. In addition, CVS Health has launched a national smoking cessation campaign that focuses on risk assessment, education, appropriate medication therapy, and long-term coaching. The various components of the treatment team—pharmacists, nurse practitioners, digital and online assets, and marketing resources—are employed in tandem to provide patients with the best opportunity to stop smoking. Smoking cessation collaboration is offered to major health-system affiliates as an important addition to their capabilities for preventing chronic diseases.

While chronic conditions have become some of the most prevalent and expensive health issues, they are also often the most preventable and manageable. Employing a team-based approach, providers can reduce the growth of complications from chronic diseases by collaborating with CVS Health to access a myriad of healthcare management products, services, and tools. Through a deep commitment to analytical research, access to data, and primary care augmentation through MinuteClinic, CVS Health is uniquely positioned to support providers in improving health outcomes and reducing medical costs. **EBDM**

CVS Health's MinuteClinic offers services that complement a patient's primary care.

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