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Evidence-Based Diabetes Management

Provider Perspective

Innovations on the Horizon for the Treatment of Type 2 Diabetes

An Interview With Javier Morales, MD

By Stanton R. Mehr

Javier Morales, MD

Evidence-Based Diabetes Management: **The scope of challenges we face in patients with type 2 diabetes mellitus (T2DM) today is extremely broad. Let's start with the state of care today. For patients who have been diagnosed and are undergoing treatment, approximately what proportion of these patients reach target glycemic levels?**

Javier Morales, MD: It varies based on the patient's age and comorbidities. One factor that has affected our attempts to reach target glycemic levels is the increased mortality as-

(continued on page 189)

Technology

Diabetes Apps: Impacting Patients' Lives

Maximizing the Use of Mobile Applications for Patients with Diabetes Mellitus

Krisy-Ann Thornby, PharmD, and Nicole Edquist, PharmD

Krisy-Ann Thornby, PharmD

Nicole Edquist, PharmD

Diabetes is a complex condition which requires various treatment and education strategies to achieve goals beyond glycemic control. Key pillars in the management of diabetes include maintaining adequate lifestyle habits, diabetes self-management education, and prevention of diabetic complications.[1] A core issue facing today's patients living with diabetes is the daunting task of tracking countless glucose readings, lab tests, medication compliance, insulin dosing, appointments, dietary intake, exercise activities, and recommendations given by various healthcare providers.

In the age of the smartphone, numerous mobile applications have been and will continue to be developed to help patients manage diabetes. A recent survey showed that in the United States, approximately 45% of adults and 34% of young adults own a smartphone.[2] The smartphone revolution provides an emerging opportunity for healthcare professionals to counsel patients on a new and potentially more effective method for electronically documenting essential health information.

(continued on page 188)

Commentary

Comparative Effectiveness Research and Formulary Placement: The Case of Diabetes

Michael E. Chernew, PhD; Rick McKellar, BS; Wade Aubry, MD; Roy Beck, MD, PhD; Joshua Benner, PharmD, ScD; Jan E. Berger, MD, MJ; A. Mark Fendrick, MD; Felicia Forma, BSc; Dana Goldman, PhD; Anne Peters Harmel, MD; Rebecca Killion, MA; Darius Lakdawalla, PhD; Douglas K. Owens, MD; and Joe Stahl, MA

Michael E. Chernew, PhD

As the nation transforms its healthcare system—with or without the Affordable Care Act (ACA)—it must face the challenge of how to maintain, or even improve, the quality of care. This requires the system to be more nuanced; to encourage use of those healthcare services that produce greater health and discourage the use of those that produce less. Implementation of this simple idea requires first identifying the clinical benefit associated with different services.

Unfortunately, we cannot always identify when services improve health, as health benefit is dependent on the specific clinical scenario and patient population. In diabetes care, this is often borne out by the existence

(continued on page 190)

Also in this issue...

AJMC TV

Harlan Krumholz, MD, discusses health policy and prevention.

Dr Peter Salgo, joined by David Calabrese, RPh, MHP and Drs Kenneth L Schaecher, Yehuda Handelsman, and Michael Weber discuss the relationship between cardiovascular health and cardiometabolic comorbidities.

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For appropriate patients with type 2 diabetes

NOW AVAILABLE: JANUMET XR

Same powerful efficacy as JANUMET (sitagliptin/metformin HCl), now available with convenient **once-daily** dosing

JANUMET XR is indicated, as an adjunct to diet and exercise, to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin extended-release is appropriate.

JANUMET XR should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

JANUMET XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while taking JANUMET XR.

Selected Important Risk Information

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, JANUMET XR should be discontinued and the patient hospitalized immediately *[see Warnings and Precautions]*.

JANUMET XR is contraindicated in patients with renal impairment (serum creatinine levels ≥1.5 mg/dL in men and ≥1.4 mg/dL in women or abnormal creatinine clearance); hypersensitivity to metformin hydrochloride; acute or chronic metabolic acidosis, including diabetic ketoacidosis; or history of a serious hypersensitivity reaction to JANUMET XR or sitagliptin, such as anaphylaxis or angioedema.

Temporarily discontinue JANUMET XR in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. Avoid use in patients with hepatic disease. Temporarily discontinue for intercurrent serious conditions, infection, or surgery.

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis.

Measure renal function before initiation of therapy with JANUMET XR and at least annually thereafter. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and JANUMET XR discontinued if evidence of renal impairment is present.

Lactic acidosis is fatal in approximately 50% of cases. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications.

Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking JANUMET XR. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis.

There have been postmarketing reports of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin with or without metformin. After initiating JANUMET XR, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue JANUMET XR and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while taking JANUMET XR.

Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving JANUMET XR.

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, JANUMET XR should be temporarily discontinued at the time of or before the procedure, withheld for 48 hours subsequent to the procedure, and reinstituted only after renal function has been re-evaluated and found to be normal.

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

Use With Medications Known to Cause Hypoglycemia

Sitagliptin

When sitagliptin was used in combination with a sulfonylurea or insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or insulin. Therefore, patients also receiving insulin or an insulin secretagogue (eg, sulfonylurea) may require a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.

The incidence (and rate) of hypoglycemia based on all reports of symptomatic hypoglycemia were: 16.4% (0.82 episodes/patient-year) for sitagliptin 100 mg in combination with metformin and glimepiride, 0.9% (0.02 episodes/patient-year) for placebo in combination with metformin and glimepiride, 8.2% (0.61 episodes/patient-year) for placebo in combination with metformin and insulin, and 15.3% (0.98 episodes/patient-year) for sitagliptin in combination with metformin and insulin.

Adverse reactions with sitagliptin in combination with metformin and rosiglitazone through Week 18 were: upper respiratory tract infection (sitagliptin, 5.5%; placebo, 5.2%) and nasopharyngitis (6.1%, 4.1%). Through Week 54 they were: upper respiratory tract infection (sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%).

Metformin hydrochloride

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects.

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUMET XR, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUMET XR, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP-4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUMET XR.

In clinical studies, the most common adverse reactions reported, regardless of investigator assessment of causality, in ≥5% of patients treated with either sitagliptin in combination with metformin or placebo were as follows: diarrhea (7.5% vs 4.0%), upper respiratory tract infection (6.2% vs 5.1%), and headache (5.9% vs 2.8%). In patients treated with sitagliptin in combination with metformin and sulfonylurea or placebo in combination with metformin and sulfonylurea: hypoglycemia (16.4% vs 0.9%) and headache (6.9% vs 2.7%). In patients treated with sitagliptin in combination with metformin and insulin or placebo in combination with metformin and insulin: hypoglycemia (15.3% vs 8.2%). Other adverse events with an incidence of ≥5% included nasopharyngitis for sitagliptin monotherapy and hypoglycemia (13.7% vs 4.9%), diarrhea (12.5% vs 5.6%), and nausea (6.7% vs 4.2%) for extended-release metformin vs placebo when added to glyburide.

Please see the adjacent Brief Summary of the Prescribing Information, including the Boxed Warning about lactic acidosis.

For more information, please visit JanumetXR.com

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 DIAB-1042703-0000 06/12 **JanumetXR.com**

ONCE-DAILY

Janumet® XR

(sitagliptin and metformin HCl extended-release) tablets

Brief Summary of Prescribing Information

JANUMET® XR (sitagliptin and metformin HCl extended-release) Tablets

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, JANUMET XR should be discontinued and the patient hospitalized immediately.
[See Warnings and Precautions.]

Important Limitations of Use. JANUMET XR should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. JANUMET XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUMET XR. *[See Warnings and Precautions.]*

CONTRAINDICATIONS

JANUMET XR is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia *[see Warnings and Precautions].*
- Hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to JANUMET XR or sitagliptin, such as anaphylaxis or angioedema. *[See Warnings and Precautions; Adverse Reactions.]*

WARNINGS AND PRECAUTIONS

Lactic Acidosis. *Metformin hydrochloride.* Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET XR and is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate concentrations (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years. In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking JANUMET XR. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. JANUMET XR treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, JANUMET XR should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, JANUMET XR should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking JANUMET XR, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, JANUMET XR should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent metabolic acidosis (in controlled trials, 32% and 67% for adjunctive treatment in adults and pediatric patients, respectively, and 15 to 25% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 20 mEq/L; 3% and 11% for adjunctive treatment in adults and pediatric patients, respectively, and 1 to 7% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 17 mEq/L) and may exacerbate the risk of metformin-induced lactic acidosis. *[See Drug Interactions; Clinical Pharmacology.]* The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis.

Patients should be educated to promptly report these symptoms to their physician should they occur. If present, JANUMET XR should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Once a patient is stabilized on any dose level of JANUMET XR, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to recur. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking JANUMET XR do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly-controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking JANUMET XR, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. *[See Contraindications.]*

Pancreatitis. There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin with or without metformin. After initiation of JANUMET XR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUMET XR should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUMET XR.

Impaired Hepatic Function. Since impaired hepatic function has been associated with some cases of lactic acidosis, JANUMET XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Assessment of Renal Function. Metformin and sitagliptin are substantially excreted by the kidney.

Metformin hydrochloride. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, JANUMET XR is contraindicated in patients with renal impairment.

Before initiation of JANUMET XR and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and JANUMET XR discontinued if evidence of renal impairment is present.

Sitagliptin. There have been postmarketing reports of worsening renal function in patients taking sitagliptin with or without metformin, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with JANUMET XR and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and JANUMET XR discontinued if evidence of renal impairment is present.

Vitamin B_{12} Levels. In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on JANUMET XR and any apparent abnormalities should be appropriately investigated and managed. *[See Adverse Reactions.]*

Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year intervals may be useful.

Alcohol Intake. Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving JANUMET® XR (sitagliptin and metformin HCl extended-release) tablets.

Surgical Procedures. Use of JANUMET XR should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes. A patient with type 2 diabetes previously well controlled on JANUMET XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, JANUMET XR must be stopped immediately and other appropriate corrective measures initiated.

Use with Medications Known to Cause Hypoglycemia. *Sitagliptin.* When sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin *[see Adverse Reactions].* Therefore, patients also receiving an insulin secretagogue (e.g., sulfonylurea) or insulin may require a lower dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia *[see Dosage and Administration].*

Metformin hydrochloride. Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs.

Concomitant Medications Affecting Renal Function or Metformin Disposition. Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion *[see Drug Interactions]*, should be used with caution.

Radiologic Studies with Intravascular Iodinated Contrast Materials. Intravascular contrast studies with iodinated materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography [CT] scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin *[see Contraindications].* Therefore, in patients in whom any such study is planned, JANUMET XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure, and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic States. Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on JANUMET XR therapy, the drug should be promptly discontinued.

Loss of Control of Blood Glucose. When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold JANUMET XR and temporarily administer insulin. JANUMET XR may be reinstituted after the acute episode is resolved.

Hypersensitivity Reactions. There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUMET XR. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUMET XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. *[See Adverse Reactions.]*

Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP-4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUMET XR.

Macrovascular Outcomes. There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET XR or any other anti-diabetic drug.

ADVERSE REACTIONS

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.

Sitagliptin and Metformin Immediate-Release Co-administration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise. The most common (≥5% of patients) adverse reactions reported (regardless of investigator assessment of causality) in a 24-week placebo-controlled factorial study in which sitagliptin and metformin immediate-release were co-administered to patients with type 2 diabetes inadequately controlled on diet and exercise were diarrhea (sitagliptin + metformin immediate-release [N=372], 7.5%; placebo [N=176], 4.0%), upper respiratory tract infection (6.2%, 5.1%), and headache (5.9%, 2.8%).

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Immediate-Release Alone. In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily metformin immediate-release regimen, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse reactions was similar to the placebo treatment group (sitagliptin and metformin immediate-release, 1.9%; placebo and metformin immediate-release, 2.5%).

Gastrointestinal Adverse Reactions. The incidences of pre-selected gastrointestinal adverse experiences in patients treated with sitagliptin and metformin immediate-release were similar to those reported for patients treated with metformin immediate-release alone.

Table 1: Pre-selected Gastrointestinal Adverse Reactions (Regardless of Investigator Assessment of Causality) Reported in Patients with Type 2 Diabetes Receiving Sitagliptin and Metformin Immediate-Release

	Number of Patients (%)					
	Study of Sitagliptin and Metformin Immediate-Release in Patients Inadequately Controlled on Diet and Exercise				Study of Sitagliptin Add-on in Patients Inadequately Controlled on Metformin Immediate-Release Alone	
	Placebo	Sitagliptin 100 mg once daily	Metformin Immediate-Release 500 mg or 1000 mg twice daily*	Sitagliptin 50 mg bid + Metformin Immediate-Release 500 mg or 1000 mg twice daily*	Placebo and Metformin Immediate-Release ≥1500 mg daily	Sitagliptin 100 mg once daily and Metformin Immediate-Release ≥1500 mg daily
	N=176	N=179	N=364	N=372	N=237	N=464
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)	6 (2.5)	11 (2.4)
Nausea	2 (1.1)	2 (1.1)	20 (5.5)	18 (4.8)	2 (0.8)	6 (1.3)
Vomiting	1 (0.6)	0 (0.0)	2 (0.5)	8 (2.2)	2 (0.8)	5 (1.1)
Abdominal Pain†	4 (2.3)	6 (3.4)	14 (3.8)	11 (3.0)	9 (3.8)	10 (2.2)

*Data pooled for the patients given the lower and higher doses of metformin.
†Abdominal discomfort was included in the analysis of abdominal pain in the study of initial therapy.

Sitagliptin in Combination with Metformin Immediate-Release and Glimepiride. In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin immediate-release and glimepiride (sitagliptin, N=116; placebo, N=113), the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: hypoglycemia (see Table 2) and headache (6.9%, 2.7%).

Sitagliptin in Combination with Metformin Immediate-Release and Rosiglitazone. In a placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin immediate-release and rosiglitazone (sitagliptin, N=181; placebo, N=97), the adverse reactions reported regardless of investigator assessment of causality

through Week 18 in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (sitagliptin, 5.5%; placebo, 5.2%) and nasopharyngitis (6.1%, 4.1%). Through Week 54, the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%).

Sitagliptin in Combination with Metformin Immediate-Release and Insulin. In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin immediate-release and insulin (sitagliptin, N=229; placebo, N=233), the only adverse reaction reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycemia (Table 2).

Hypoglycemia. In all (N=5) studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required although most (77%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL. When the combination of sitagliptin and metformin immediate-release was co-administered with a sulfonylurea or with insulin, the percentage of patients reporting at least one adverse reaction of hypoglycemia was higher than that observed with placebo and metformin immediate-release co-administered with a sulfonylurea or with insulin (Table 2).

Table 2: Incidence and Rate of Hypoglycemia* (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Clinical Studies of Sitagliptin in Combination with Metformin Immediate-Release Co-administered with Glimepiride or Insulin

Add-On to Glimepiride + Metformin Immediate-Release (24 weeks)	**Sitagliptin 100 mg + Metformin Immediate-Release + Glimepiride**	**Placebo + Metformin Immediate-Release + Glimepiride**
	N=116	N=113
Overall (%)	19 (16.4)	1 (0.9)
Rate (episodes/patient-year)†	0.82	0.02
Severe (%)‡	0 (0.0)	0 (0.0)
Add-On to Insulin + Metformin Immediate-Release (24 weeks)	**Sitagliptin 100 mg + Metformin Immediate-Release + Insulin**	**Placebo + Metformin Immediate-Release + Insulin**
	N=229	N=233
Overall (%)	35 (15.3)	19 (8.2)
Rate (episodes/patient-year)†	0.98	0.61
Severe (%)‡	1 (0.4)	1 (0.4)

*Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required: Intent-to-treat population.

†Based on total number of events (i.e., a single patient may have had multiple events).

‡Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

The overall incidence of reported adverse reactions of hypoglycemia in patients with type 2 diabetes inadequately controlled on diet and exercise was 0.6% in patients given placebo, 0.6% in patients given sitagliptin alone, 0.8% in patients given metformin immediate-release alone, and 1.6% in patients given sitagliptin in combination with metformin immediate-release. In patients with type 2 diabetes inadequately controlled on metformin immediate-release alone, the overall incidence of adverse reactions of hypoglycemia was 1.3% in patients given add-on sitagliptin and 2.1% in patients given add-on placebo.

In the study of sitagliptin and add-on combination therapy with metformin immediate-release and rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on sitagliptin and 0.0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on sitagliptin and 1.0% in patients given add-on placebo.

Vital Signs and Electrocardiograms. With the combination of sitagliptin and metformin immediate-release, no clinically meaningful changes in vital signs or in electrocardiogram parameters (including the QTc interval) were observed.

Pancreatitis. In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control). *[See Warnings and Precautions.]*

Sitagliptin. The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo was nasopharyngitis.

Metformin Extended-Release. In a 24-week clinical trial in which extended-release metformin or placebo was added to glyburide therapy, the most common (>5% and greater than placebo) adverse reactions in the combined treatment group were hypoglycemia (13.7% vs. 4.9%), diarrhea (12.5% vs. 5.6%), and nausea (6.7% vs. 4.2%).

Laboratory Tests

Sitagliptin. The incidence of laboratory adverse reactions was similar in patients treated with sitagliptin and metformin immediate-release (7.6%) compared to patients treated with placebo and metformin (8.7%). In most but not all studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs. placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to a small increase in neutrophils. This change in laboratory parameters is not considered to be clinically relevant.

Metformin hydrochloride. In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. *[See Warnings and Precautions.]*

Postmarketing Experience. Additional adverse reactions have been identified during postapproval use of sitagliptin with or without metformin, and/or in combination with other antidiabetic medications. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome *[see Warnings and Precautions]*; upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis *[see Indications and Usage; Warnings and Precautions]*; worsening renal function, including acute renal failure (sometimes requiring dialysis) *[see Warnings and Precautions]*; constipation; vomiting; headache.

DRUG INTERACTIONS

Carbonic Anhydrase Inhibitors. Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with JANUMET® XR (sitagliptin and metformin HCl extended-release) tablets, as the risk of lactic acidosis may increase.

Cationic Drugs. Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JANUMET XR and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

The Use of Metformin with Other Drugs. Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JANUMET XR the patient should be closely observed to maintain adequate glycemic control.

USE IN SPECIFIC POPULATIONS

Pregnancy. *Pregnancy Category B.*

JANUMET® XR (sitagliptin and metformin HCl extended-release) tablets. There are no adequate and well-controlled studies in pregnant women with JANUMET XR or its individual components; therefore, the safety of JANUMET XR in pregnant women is not known. JANUMET XR should be used during pregnancy only if clearly needed.

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a registry to monitor the pregnancy outcomes of women exposed to JANUMET XR while pregnant. Health care providers are encouraged to report any prenatal exposure to JANUMET XR by calling the Pregnancy Registry at 1-800-986-8999.

No animal studies have been conducted with the combined products in JANUMET XR to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

Sitagliptin. Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies with sitagliptin in pregnant women.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30 and 20 times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

Metformin hydrochloride. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, which represent 3 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, metformin hydrochloride should not be used during pregnancy unless clearly needed.

Nursing Mothers. No studies in lactating animals have been conducted with the combined components of JANUMET XR. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin or metformin are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUMET XR is administered to a nursing woman.

Pediatric Use. Safety and effectiveness of JANUMET XR in pediatric patients under 18 years have not been established.

Geriatric Use. *JANUMET XR.* Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUMET XR should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. *[See Warnings and Precautions; Clinical Pharmacology.]*

Sitagliptin. Of the total number of subjects (N=3884) in premarketing Phase II and III clinical studies of sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride. Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin should only be used in patients with normal renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function. *[See Contraindications; Warnings and Precautions; Clinical Pharmacology.]*

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Janumet® XR
(sitagliptin and metformin HCl extended-release) tablets

This spring, the American Diabetes Association (ADA) released a study that confirmed what many healthcare providers and payers knew intuitively: the number of Americans living with type 2 diabetes has exploded, and so has the cost of caring for them. The ADA found that diabetes had cost the country $245 billion in 2012 in financial burden, healthcare, and lost productivity—a figure that was 41% higher than just 5 years ago. Not only are 26 million adults and children living with the disease, but another 79 million have health conditions that put them at risk of developing type 2 diabetes someday. Not surprisingly, diabetes has replaced smoking as the primary driver of healthcare costs. And yet, the share of medical spending that went for antidiabetic agents and supplies was precisely the same in 2007 and 2012, just 12%. Apparently, as a nation we are spending far more on the consequences of diabetes. How sobering, given that 62% of all diabetes care in the United States is funded with government insurance (eg, Medicare, Medicaid, or military health plans).

With this issue of *Evidence-Based Diabetes Management,* and our efforts at *The American Journal of Managed Care* to bring together leaders in the communities of healthcare providers, policy makers, and payers, we are confronting this epidemic with the best information available. Javier Morales, MD, discusses new approaches for treatment, and Brice Labruzzo Mohundro, PharmD, takes us through what is in the pharmaceutical pipeline. A study led by Precision Health Economics and lead author Katalin Bognar, PhD, examines patient outcomes associated with newer and older classes of diabetes medication. And this issue has tools and information for getting patients to stick with a treatment plan.

While the costs associated with diabetes soared from 2007 to 2012, the share of medical spending for antidiabetic agents and supplies remained just 12%.

Patient behavior is at the heart of the challenge that diabetes presents. That is why *AJMC* will join with Precision Health Economics on June 20 at the University of Chicago for a 1-day conference entitled, "Patient-Centered Diabetes Care: Future Directions." The event will be moderated by Dana Goldman, PhD, director of the Leonard D. Schaeffer Center for Health Policy and Economics at the University of Southern California. Our agenda features discussions on how physicians can better tailor care to patients, ways to unlock the value of better patient adherence, and how patient behavior impacts the quality of care and outcomes. The day will provide opportunities to foster relationships among treating physicians, creators of life-saving medications, and the payers who help our system thrive. Look forward to our special edition of the proceedings, as well as updates on www.ajmc.com.

As always, thank you for reading.

Brian Haug
Publisher

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

In This Issue...

THE AMERICAN JOURNAL OF MANAGED CARE

Researchers are investigating the use of bupropion and naltrexone in combination to produce significant weight loss.
Brice Labruzzo Mohundro, PharmD, BCACP

Mobile apps for managing diabetes focus on 3 areas: glucose control, medication logs, and food tracking.

"The incretins are here to stay; they're a no-brainer."
Javier Morales, MD

Studies have shown that the spending offset associated with better drug adherence may be significant. Raising Medicare costs was associated with a 6% greater likelihood of hospitalization.

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BMI and Beyond: Identifing Obesity in Patients at Risk for Diabetes and Heart Disease

Marj P. Zimmerman, MS, BSPharm, and Stanton R. Mehr

Obesity continues to be a health and economic challenge for the United States, and the condition is a known contributor to rising US healthcare costs.[1] To address this issue, better methods are needed to define who is obese and how the condition puts a person's health in jeopardy, as well as greater use of these methods among clinicians. Definitions vary among professional organizations, even though members agree obesity is a major predictor of health risk. Reaching a consensus on the best way to measure obesity would be a good foundation for initiating a strategy to reduce its risks.

Obesity has risen in recent decades among both children and adults. According to National Health and Nutrition Examination Survey data, approximately 36% of adults (78 million) and 17% of children and adolescents (~12.5 million) were considered obese according to a survey for the period covering 2009-2010. (The multidecade rise in obesity appears to be leveling off, however.) People older than 60 years are more likely to be obese than younger persons, but an appreciable difference in the obesity rate between men and women could not be discerned.[2,3]

As we will discuss, the use of the ratio known as the body mass index (BMI) can be an imperfect way to measure whether a person is overweight or obese. However, this measure is used by the Centers for Disease Control and Prevention (CDC) to track data on obesity and overweight nationally and by state. Thus, it is worth understanding that the CDC considers a person with a BMI measurement of 30 kg/m^2 or greater to be obese, while a person with a measurement of 25 to 29.9 kg/m^2 is considered overweight.[4] We will review how this ratio is calculated below.

Besides those classified as obese, an additional 33% of adults are classified as overweight.[5] Sixty-seven percent of whites are considered to be overweight or obese, compared with 77% of African Americans and 79% of Hispanics. Asian Americans, American Indians, Alaska Natives, and Native Hawaiians or other Pacific Islanders record lower rates of obesity (12%, 40%, and 44%, respectively).[6] Obesity is associated with several diseases, most notably heart disease, stroke, type 2 diabetes mellitus, asthma, gallbladder disease, sleep apnea, and some types of cancer.[7,8] The costs of these comorbidities and complications are substantial. In 2005 dollars, estimated medical costs were $190.2 billion, representing about 21% of health expenditures.[9] If the rate of obesity among the US population continues unchecked, it is projected that obesity-related medical costs could rise by $48 to $66 billion a year by 2030.[10] It had been believed that obesity led to a higher rate of mortality, but newer research has reached a different conclusion. Thus, there is an obesity paradox, whereby people meeting the criteria for obesity sometimes have survival benefits over those of normal weight.[11] However, the presence of a "U/J" curve is controversial. These findings may mean that the definition of obesity needs to be updated. More importantly, it demonstrates that the magnitude of health risks is the parameter that needs to be measured—not necessarily the weight of a patient.

Defining Obesity and Assessing Health Risk

Obesity is associated with an excess amount of body fat. The most accurate way of measuring fat is to weigh an individual underwater or in a vessel that measures the amount of air displaced; or using dual-energy X-ray absorptiometry (DEXA). Of course, these methods are not practical and their increased utilization can result in substantially higher costs. Another method involves using calipers to measure fat at various sites on the body (which differ between males and females); this is useful if performed by people experienced with conducting such procedures. Bioelectrical impedance testing is another means of measuring the composition of patients' bodies. These methods are also considered impractical.

Various other methods are being used to assess health risks in those with obesity. Interestingly, interpretations of the ranges and the associated risks vary with each of the following assessments.

BMI. Body mass index (BMI) is widely used to estimate obesity; however, it does not directly measure body fat or muscle. It is considered a good predictor of risk for diseases that can or do occur with obesity. BMI is a ratio of weight to height calculated with a formula[12]:

$$\text{BMI} = \text{weight (kg)}/[\text{height (m)}]^2$$

Classifications of BMI are shown in Table 1 for adults 20 years and older. This method may overestimate body fat in individuals with a muscular build or in athletes. Conversely, this method may underestimate body fat in older individuals or in people who have lost muscle mass. The BMI score over 30 kg/m^2 has now been further broken down to include classes of obesity as well as designating extreme obesity (**Table 1**).

Waist Circumference (WC). This method is calculated by measuring an individual's waist. A tape measure would be placed around the middle of the individual just above the hip bones or 1 inch above the navel and the measurement taken just after the individual exhales. For women, a WC measurement of over 35 inches (>102 cm) and for men, a WC of more than 40 inches (>88 cm) indicates high risk of diabetes and heart disease (**Table 2**).[12]

Waist-to-Height Ratio (WHtR). This method is useful for individuals who have a higher percentage of muscle and a lower percentage of fat, or for women who have a pear rather than an apple shape. A WHtR under 50% is considered healthy. Table 2 assumes the average man is 69 inches in height and the average woman is 64 inches in height.[13,14]

Table 1. BMI and Obesity Classifications in Adults

Classification by BMI		BMI (kg/m^2)
Underweight		<18.5
Healthy weight		18.5-24.9
Overweight		25.0-29.9
Obese		≥30.0
Obesity Status	**BMI (kg/m^2)**	**Obesity Class**
Obese	30.0-34.9	I
	35.0-39.9	II
Extremely Obese	≥40.0	III

BMI indicates body mass index.

Table 2. Risk of Diabetes and Heart Disease Utilizing the WHtR

	Increased Diabetes and Heart Disease Risk Waist Circumference (WHtR)	Substantially Increased Diabetes and Heart Disease Risk Waist Circumference (WHtR)
Men	≥37.0 inches (0.53)	≥40.2 inches (0.58)
Women	≥31.5 inches (0.49)	≥34.6 inches (0.54)

WHtR indicates waist to height ratio.

Table 3. Obesity and Risk Classifications by BMI and WC Measures Combined

Clinical Classification	BMI (kg/m²)	Obesity Class	Disease Risk[a] Relative to Normal Weight and Waist Circumference	
			Men ≤40 in Women ≤35 in	Men >40 in Women >35 in
Underweight	<18.5			
Normal	18.5-24.9			
Overweight	25.0-20.9		Increased	High
Obesity	30.0-34.9	I	High	Very High
	35.0-39.9	II	Very High	Very High
Extreme obesity	≥40	III	Extremely High	Extremely High

[a]Disease risk for type 2 diabetes mellitus, hypertension, and cardiovascular disease.

Waist-to-Hip Ratio (WHR). This calculation is made by dividing the waist circumference by the hip circumference measurement. A WHR of 1.0 is considered to put an individual at risk, whether male or female. A WHR ≤0.90 for men and ≤0.80 for women is considered healthy.[15]

Combined BMI and WC. Another strategy to use for assessing risk may be to combine BMI and the waist circumference (**Table 3**).[12]

A Body Shape Index (ABSI). This methodology for defining health risks uses WC, weight, and height and considers the central concentration of adiposity.[16] It is calculated as:

$$ABSI = \frac{WC}{BMI^{2/3}\,Height^{1/2}}$$

A chart would need to be used so that the calculation could easily be determined.

Evolving Measures of Obesity and Risk for Diabetes

The connection between obesity, as defined by BMI, and type 2 diabetes mellitus (T2DM) is well accepted by the medical community. Observations have confirmed that abdominal obesity is an important risk factor, even when controlling for age, family history, and smoking habits for developing T2DM.[17] However, predicting which overweight or obese patients will eventually develop T2DM is less well supported by evidence.[18]

In an effort to further define who is most at risk, studies have been undertaken to determine a relationship between measures of obesity and the risk of developing T2DM, utilizing various methods for defining obesity, including BMI, WC, WHR, WHtR, and body fat percentage. The studies have yielded mixed results.

Between 1986 and 1992, a study of male health professionals aged 40 to 75 years revealed that BMI, WC, and WHR were all predictors for developing T2DM. There was a stronger relationship for individuals with BMI levels of at least 24 kg/m² compared with those with a BMI below 23 kg/m² and an even higher risk for those with a BMI of 29 kg/m² or more. Waist circumference was observed to be a greater risk than WHR, related in part to the potential errors associated with measuring and calculating WHR. Owing to the positive correlation observed with WC and developing T2DM, the authors concluded that WC may become an important risk factor for T2DM especially in lean men, but that BMI was the most important risk factor.[19]

According to another epidemiologic study of patients with a family history of diabetes mellitus, the greatest relative risk for developing diabetes was associated with abnormal WHtR measures rather than high BMIs or WCs.[20]

When considering a family history for abnormal glucose tolerance, high measurements for WHtR and WC were significantly more associated with developing T2DM than an elevated BMI. However, for individuals with a BMI of 27 kg/m² or higher, WHtR and WC measures were found to be a poorer predictor of risk than BMI. Limitations of this study were that it only included men, and the duration of observation was only 3.6 years.[20]

French researchers who studied men and women aged 40 to 64 years for 5 years could not find any significant difference between using the BMI, WC, and WHR to predict risk of diabetes. Those developing diabetes did have significantly higher BMI, WHR, and WC measurements as well a stronger family history of diabetes than those who did not develop diabetes. Researchers concluded that the 30% of the population who are more obese should be screened for type 2 diabetes, and that the most convenient method should be used.[21]

A meta-analysis of the literature conducted in 2006 concluded that BMI, WC, and WHR yielded similar predictive accuracies for the development of diabetes, with WC and WHR having a slightly better relative risk predication. Another meta-analysis by the same research group produced similar results, with WC being a slightly better predictor of risk for developing T2DM than BMI.[22]

The Obesity Society, the American Society for Nutrition, and the American Diabetes Association (NAASO) developed a consensus statement in 2007 that concluded that: (1) Waist circumference is a good predictor of diabetes risk, (2) it has incremental value beyond BMI in predicting diabetes, and (3) measuring WC may identify individuals who have an increased cardiometabolic risk, but these patients would not be managed differently from those with a BMI of at least 25 kg/m². Thus, they concluded that for clinical practice, the implications of the WC measurement are somewhat limited, and additional analyses are needed to define the future role of WC.[23]

When looking at a limited population group, especially with homogeneous race and ethnicities, WHR and WC seem to be better indicators than BMI for predicting the development of T2DM. When generalizing this to a larger diverse population, both elevated BMIs and WCs seem to be independent risk factors for T2DM development.[17,24]

A recent study comparing various measures of body composition (including WC, WHtR, percent body fat, fat-free mass index, and BMI for predicting metabolic syndrome) comprised more than 12,000 patients over 1 year. No measurements were consistently better in predicting metabolic syndrome than BMI. Additionally, these researchers could not find any differences based on race or ethnicity; however, all of the associations were stronger for women than men. This analysis disputed the presence of a U/J curve, but that may be attributable to the low number of individuals with low body fat and also that the participants were all employed—which potentially excluded people unable to work due to sickness and an accompanying low body fat percentage.[25]

It appears that the optimal way to measure risk of diabetes mellitus may vary among different age groups and races/ethnic groups.[26]

A measurement of body fat, one that is not easily performed in the clinical setting, may provide a better insight about the risk for developing T2DM than BMI or WC. Persons with a BMI below 25 kg/m² who had higher percentages of body fat had an increased risk for developing T2DM. Body fat was greater in both lean men and women (as defined by BMI) who were diagnosed with prediabetes or T2DM.[27]

Obesity Compared With Metabolic Abnormalities for Coronary Heart Disease Risk

Metabolic syndrome criteria usually include obesity or high WC measures. In order to determine whether metabolic syndrome is a major contributor to the incidences of cardiovascular disease and stroke, only metabolic syndrome criteria were utilized in the study. There were 4 study groups: (1) patients who had no metabolic syndrome components or diabetes, (2) those who had 1 or 2 metabolic syndrome components, (3) patients with at least 3 metabolic syndrome components and no diabetes, and (4) patients with diabetes. This cohort was compared with individuals exhibiting abdominal obesity (WC in men >102 cm, in women >88 cm). The study suggested that having any metabolic abnormality is a stronger predictor of coronary heart disease and stroke than having abdominal obesity.[28]

Measures of Obesity and Cardiovascular Risk and Overall Mortality Risk

There is a strong link between obesity and risk for cardiovascular disease as well as for overall mortality. The individual importance of BMI, WHR, and WC has been the basis for research. Results of the research have shown conflicting results. Some studies have shown that WHR is a better predictor of obesity-associated risk than BMI, while others have shown that WC is a better predictor than BMI.[29,30]

Combining BMI and WC has been suggested as a better predictor of cardiovascular risk than either measure alone.[31] Another study provided mixed results and led to the conclusion that if WC had any predictive value for cardiovascular risk, it was modest. In overweight women (BMI, 25–30 kg/m²), researchers found that combining BMI and WC may help identify those at cardiovascular risk, but this was not found to be the case in women with normal or very high BMI or men of any BMI level.[32]

Both WC and WHR are indicative of an increased risk for all-cause mortality independent of the BMI. In fact, the relative risk is stronger in those with a relatively low BMI compared with those with a higher BMI. It has been suggested that WC could replace both BMI and WHR as a single risk factor for all-cause mortality.[33] Similar results were seen in another study in which all-cause mortality risk was predicted by both WC and WHR, with the highest risk of

all-cause mortality predicted by WC no matter the BMI.[34]

To further add to the complexity of associating the risk of cardiac disease and mortality with measurements of obesity, an analysis of data involving patients with confirmed coronary artery disease led to further evidence of the importance of WC and WHR measurements. Individuals with a normal BMI who had an elevated WC or WHR had higher mortality compared with those with a BMI that meets the criteria of being overweight or obese and a normal WC or WHR measure. These findings indicate that BMI and a measure of central adiposity should both be utilized, especially in individuals with coronary artery disease.[35]

Measures of Obesity and Healthcare Costs

A study in the early part of last decade noted that a greater BMI or WC were associated with increased total healthcare costs. In this same study, they also determined that total healthcare costs correlate better with abnormal WCs than with high BMIs and that WC is an independent predictor of costs. Individuals in the highest WC quartile had the highest healthcare costs and the greater costs in all quartiles versus BMI; the incremental healthcare costs were primarily the result of inpatient charges.[36] Another study found that WC is a more sensitive measure for identifying individuals with relatively high healthcare costs. When analyzing subsets of patients, investigators discovered that even considering persons with a normal BMI, costs increased when the WC measures increased or substantially increased (women ≥80 and 88 cm, men ≥94 and 102 cm) compared with individuals with normal WCs (<80 cm women, <94 cm men) and these costs were greater than in individuals who were considered overweight or obese and had normal WCs. Thus, the greater the abdominal adiposity, the greater the likelihood of higher healthcare costs.[37]

Body weight has also been found to affect indirect costs, specifically absence from work resulting from obesity-related health problems. High BMI, WC, or WHR were predictive of work absences, with WHR having the lowest relative predictive accuracy.[38]

Conclusion

Obesity remains a risk factor for a number of diseases, including T2DM and cardiovascular disease, and it influences all-cause mortality. The best measure of obesity continues to elude the healthcare community. However, it is of the utmost importance that a consistent, easily available tool is utilized and if possible, a measure of central adiposity be utilized as well. This is a challenge at the practice level, but educating patients about the importance of these measures of obesity can be the basis for determining the method(s) best suited for them to reach their weight/shape targets. **EBDM**

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Payer Perspective

Each Patient Encounter an Opportunity for Obesity Measurement

Gary M. Owens, MD

According to the Centers for Disease Control and Prevention, 36% of adults and 17% of children in the US population are obese.[1] The epidemic of obesity and the associated cost impact of the consequences of obesity is a topic of growing importance for payers. The reasons for this are obvious: Obesity-related illnesses are among the major cost drivers for payers. Obesity-related conditions include heart disease, stroke, type 2 diabetes, and certain types of cancer, some of the leading causes of death in America. In 2008, medical costs associated with obesity were estimated at $147 billion; the medical costs paid by third-party payers for people who are obese were $1429 higher than for those of normal weight.[1]

In May 2012, the Institute of Medicine issued "Accelerating Progress in Obesity Prevention: Solving the Weight of the Nation." This report builds a case that the obesity epidemic is driven by both environmental changes and individual decision making. The report points out that changing environments at home, in schools, in the food and beverage industry, and even in the workplace are the major driver of the current epidemic.[2] Therefore, the management of obesity becomes not only an issue of managing individuals by the medical system, but a societal issue that must be addressed at all levels. There is no 1 simple solution to the problem, and payers, initiatives alone cannot be the solution.

However, payers need to take a leading role in managing the impact of obesity. Payers are in a unique position to allow them to integrate the needs of multiple stakeholders including providers, patients (members), and employers, all of whom must play a major role in creating the societal changes described in the IOM report. Payers will need to create initiatives that incentivize providers to measure BMI or one of the alternative measurements of body fat on a consistent basis. As noted in the article by Zimmerman and Mehr,[3] there is no perfect measure of obesity. However, most standardized measures of obesity are supported by data that show the definite association of obesity with the risk of conditions like diabetes and cardiovascular disease.

Working with both their members and providers, payers will need to develop incentives for doctors to regularly include a standardized measurement of obesity in each patient encounter. Each primary office visit for the management of chronic illness, such as diabetes or heart disease, should be treated as an opportunity to discuss the impact of obesity on their illness. Payers will also need to create programs to better educate their members and create incentives for them to take personal responsibility for dietary management. And, of course, employers can play a vital role by developing benefit programs that reward healthy-eating behaviors by their employers. Further, they can create a "food-healthy" environment at their worksite cafeterias and vending machines.

Ultimately, the epidemic of obesity is a societal problem and all sectors of society will need to be engaged in the solution. Payers have the unique opportunity to engage their members and their customers in a joint effort to combat this growing problem. Ultimately, all stakeholders will benefit from the potential for improvement in health outcomes and the associated positive impact on cost that can result from improving obesity rates.

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Gaming the System for Better Adherence

Medication nonadherence, including persistence with medical regimens, continues to vex the healthcare system. According to health policy experts, medication nonadherence not only drains the healthcare system of resources, but seriously hinders the effectiveness of important treatment innovations. A new approach to nonadherence management, however, could change this frustrating picture.

"Medicine doesn't matter, until it enters the body," stated Yelena Yankovskaya, PharmD. Yankovskaya, a fellow in managed markets at the Mayes College of Healthcare Business and Policy, University of the Sciences, Philadelphia, points out that the careful, time-consuming, and ingenious innovations created by manufacturers and scientists and the programs created to ensure access to drugs are "wasted if the patient doesn't take the drug."

Nonadherence is pervasive and accounts for nearly $317 billion annually in healthcare costs. According to Yankovskaya, patients with diabetes are key contributors, representing one-third of this figure. Preventing nonadherence is an opportunity for great cost savings.

In her presentation "Emerging Solutions for Medication Nonadherence," she provided 3 reasons why patients do not take their medication: (1) behavioral factors (69%); (2) out-of-pocket costs (16%); and (3) clinical reasons, such as medication side effects (15%). Yankovskaya noted that the behavior component may be the most difficult to address, because "Adherence can be a deep personal barrier. For instance, injecting oneself is an intense, physiologically abnormal experience."

Some payers have tried to use predictive modeling to evaluate claims data and electronic health records to identify patients who may benefit from targeted behavioral interventions. Express Scripts tried this, and found that the greatest improvements were seen with the use of "loss aversion," in which patients receive correspondence from the plan or pharmacy benefit manager that they will lose benefits or there will be a financial cost if they do not change their adherence behavior.

Perhaps the newest interesting approach to improving adherence is "gamification," said Yankovskaya, "the process of manipulating 'fun' to serve a specific purpose. This involves trying to apply what makes games fun and to trick the brain to make less pleasant tasks fun." Typically, it involves awarding points, badges, and competition to help patients change their behavior. For example, to encourage more exercise, Swedish government officials reconstructed a public stairway into a set of piano keys (in appearance and tone). When the person stepped on a stair, it would play a specific tone. The use of stairs at this location increased by 66% compared with the use of an escalator.

Apple now offers a free application called Mango, which encourages patients to take their medication. With this application, patients enter their medication regimen, and then it reminds them when it is time to take it with alerts. Each time the patient takes their medication, it awards points and the chance to win a tangible prize. The retailer Target is piloting the use of this application with its employees, and the developers hope that it will prove very useful, especially with younger patients.

Yankovskaya noted that different adherence strategies are necessary, because some may work and others may not, based on the patient type. For others, a combination of strategies, such as value-based benefit designs and behavioral strategies, will be needed. Even with games, she pointed out, people tend to get bored or disinterested, so it will be important to use gamification for medication adherence in a number of different ways. She concluded with a reminder that medicine means nothing unless we take that extra step to make sure that patients take their medication. **EBDM**

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Drugs Under Development for Cardiovascular Risk

Brice Labruzzo Mohundro, PharmD, BCACP

Cardiometabolic risk, also known as metabolic syndrome, is a collection of risk factors that increase a person's risk of developing cardiovascular (CV) disease and type 2 diabetes mellitus (T2DM). In 2009, over one-third of the US population over the age of 20 years met the criteria for having metabolic syndrome as defined by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP/ATP III).[1] Metabolic syndrome prevalence increases with age and body mass index (BMI).[1] NCEP/ATP III classified abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance with or without glucose intolerance, and proinflammatory and prothrombotic states as factors contributing to the development of CV disease.[2] Due to the nature of the aforementioned risk factors, management of cardiometabolic risk may involve both therapeutic lifestyle changes (weight loss and physical activity) and pharmacotherapy to address non-lipid and lipid risk factors.[2] The ultimate goal of both of these treatment modalities is to lower T2DM and CV risk. Pharmacologic agents used to decrease risk may include drugs for dyslipidemia and antihypertensives, as well as drugs to assist with weight loss (**Table**).

Lipids

Dyslipidemia is defined as elevated total cholesterol, elevated low-density lipoprotein cholesterol (LDL-C), or decreased high-density lipoprotein cholesterol (HDL-C). According to NCEP/ATP III reduction of LDL-C should be the primary goal of lipid management. Once goal LDL-C is achieved, focus should shift to the management of metabolic syndrome, which includes therapeutic lifestyle changes and treatment of non-HDLC. NCEP/ATP III does not specify HDL goals; however, studies suggest increasing HDL-C decreases CV risk.[2] The mainstay of LDL-C-lowering therapy has been statins since the approval of the first in-class statin, lovastatin, in the late 1980s.[3]

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Apolipoprotein B (apoB) plays an integral role in very-low-density lipoprotein (VLDL) biosynthesis, which is a precursor to LDL-C. Increased levels have been correlated with atherosclerotic disease progression, thus making it a favorable pharmacologic target.[4] Antisense oligonucleotides (ASO) are single-strand synthetic analogues of nucleic acids 8 to 50 nucleotides long, which bind via hybridization to a target ribonucleic acid. ASOs targeting apoB decrease both LDL production and progression of atherosclerosis.[4,5] In an animal model of LDL receptor–deficient mice, ISIS 147764 demonstrated LDL-lowering effects of 60% to 90% in addition to decreased aortic atherosclerosis.[4]

Mipomersen, another ASO also targeting apoB, is delivered via subcutaneous injection.[6] Mipomersen received orphan status from the US Food and Drug Administration (FDA) in January for the treatment of homozygous familial hypercholesterolemia (HoFH); however, phase II randomized placebo-controlled trials (RCTs) have also been conducted in patients with hypercholesterolemia.[5,7] Data from a small phase II dose escalation study demonstrated reduction of LDL-C ranging from 15% to 71%. Of particular note, reduction percentages seen with the higher doses exceeded reported reductions achieved by atorvastatin and rosuvastatin, the 2 most potent statins available on the market. Higher reductions in apoB levels when compared with statins were also observed. Adverse effects (AEs) occurring in greater than 10% of patients included injection site reaction, headache, nasopharyngitis, fatigue, myalgia, flu-like illness, increase in hepatic enzymes, back pain, nausea, and listlessness. Of these AEs, injection site reaction and headache were the most prevalent.[6] A phase II study evaluating the effects of mipomersen in patients intolerant to high-dose statins has been completed

Table. Drugs Currently Being Investigated to Decrease Cardiovascular Risk Factors

Date Updated	Company/ Sponsor	Product	Mechanism of Action	Indication(s)	Stage(s)	Licensee/ Partner(s)
03/04/13	Genzyme	Kynamro (mipomersen; ISIS 301012)	ASO against apo B	Homozygous familial hypercholesterolemia (HoFH)	Phase II/III	Isis Pharmaceuticals
03/29/13	Amgen	AMG-145	PCSK9 inhibitor	Hyperlipidemia	Phase II/III	N/A
03/14/13	Sanofi	SAR236553 (REGN727)	PCSK9 inhibitor	Hypercholesterolemia	Phase I/II/III	Regeneron Pharmaceuticals
01/18/13	Aegerion Pharmaceuticals, Inc	Juxtapid (lomitapide; AEGR-733)	MTP inhibitor	HoFH	Phase I/II/III	N/A
12/10/12	Surface Logix	SLx-4090	MTP inhibitor	Hyperlipidemia; hypertriglyceridemia; T2DM	Phase II	N/A
03/27/13	Merck	Anacetrapib (MK-0859)	CETP inhibitor	Dyslipidemia; hypercholesterolemia	Phase III	N/A
03/29/13	Eli Lilly and Company	Evacetrapib (LY2484595)	CETP inhibitor	Dyslipidemia	Phase I/II	N/A
02/14/13	Orexigen Therapeutics, Inc	Naltrexone SR/ bupropion SR	Opioid receptor antagonist/ dopamine and norepinephrine reuptake inhibitor	Obesity; overweight; T2DM	Phase III	N/A
11/27/12	Orexigen Therapeutics, Inc	Zonisamide SR/ bupropion SR	Anti-epileptic/ dopamine and norepinephrine reuptake inhibitor	Obesity	Phase II	N/A
03/21/13	Zafgen, Inc	Beloranib (ZGN-440)	Fumagillin analogue	Obesity; overweight; Prader-Willi syndrome	Phase II	N/A
3/26/13	Novartis Pharmaceuticals	LCZ-696	Angiotension receptor and neprilysin inhibitor	Chronic heart failure; (essential) hypertension	Phase II/III	N/A

ASO indicates antisense oligonucleotide; CETP, cholesteryl ester transfer protein; MTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9; T2DM, type 2 diabetes mellitus.

but results have not been published.[8] The results of a phase III study evaluating the effect of a mipomersen 200-mg weekly subcutaneous injection versus placebo in patients on maximally tolerated statin therapy and another hypolipidemic agent demonstrated a reduction in LDL-C from 276 mg/dL at baseline to 174 mg/dL. No statistical information was provided.[9]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are another novel class being investigated. PCSK9 is a serine protease that binds to the LDL receptor. LDL receptors with this protease attached are then degraded, thus decreasing the number of LDL receptors available on hepatocytes. Consequently, LDL-C levels increase. This effect has been observed in genetics studies performed in individuals with increased PCSK9 function, making this a potential target for patients with elevated LDL-C.[10] AMG-145 is a human monoclonal antibody to PSCK9 that inhibits PSCK9's interaction with LDL receptors and is also administered via subcutaneous injection. AMG-145 was studied in low cardiac risk patients who had not previously been on any lipid-altering medications. Patients received placebo, ezetimibe monotherapy, or varying doses of

Researchers are investigating the use of bupropion and naltrexone in combination to produce significant weight loss.

AMG-145. At week 12, when compared with placebo, significant reductions in LDL-C were seen with all doses of AMG-145. An almost 15% greater reduction in LDL was also observed when comparing AMG-145 with ezetimibe, a statistically significant reduction. Injection site reaction occurred in 6% of the patients receiving AMG-145.[10] LAPLACE-TIMI 57, a phase II RCT, evaluated AMG-145 in patients taking a statin with or without ezetimibe. LDL-C concentration at week 12 was reduced 42% to 66% in patients receiving the drug every 2 weeks and 42% to 50% in patients receiving the drug every 4 weeks. AMG-145 was well tolerated in this study.[11] REGN-727/SAR-236553, another monoclonal antibody to PCSK9, was evaluated in a phase II study in patients with heterozygous familial hypercholesterolemia. Six weeks before randomization, patients received a daily statin dose with or without ezetimibe. At week 12, REGN-727 resulted in a least squares mean reduction of 29% to 68% compared with 11% with placebo. The greatest reduction was seen with REGN 727 150 mg every 2 weeks. At week 12, 94% of patients receiving this dose achieved an LDL less than 100 mg/dL while 81% of patients achieved an LDL-C less than 70 mg/dL. Gastrointestinal disorders and injection site reactions were the most common AEs reported.[12] REGN 727 was also evaluated in combination with atorvastatin in patients with LDL-C greater than or equal to 100 mg/dL. Results from this study were in favor of the combination. After 8 weeks of treatment, the least-squares mean (± SE) difference in LDL cholesterol from baseline was −55.9 ± 4.9 when comparing participants receiving atorvastatin 80 mg plus REGN 727 and those only taking atorvastatin 80 mg.[13]

A third novel pharmacologic class targeting apoB is the microsomal triglyceride transfer protein (MTP) inhibitors. MTP transfers lipid molecules onto apoB; therefore inhibition of these proteins will lead to decreased production of chylomicrons and VLDL cholesterol, and ultimately, LDL-C.[14] Unfortunately another lipid effect of this class is decreased HDL levels with a 5% to 10% reduction reported in studies.[14] As with mipomersen, the MTP inhibitor lomitapide was provided with FDA orphan status at the end of 2012.[15] A phase III single-arm, open-label study evaluated the effects of lomitapide in patients with difficult to treat HoFH already receiving lipid-lowering therapy and apheresis. Other lipid-lowering medications were continued throughout the study. After 26 weeks of therapy, an observed reduction in LDL-C levels of 50% was observed with a median dose of lomitapide 40 mg daily. At week 56, LDL-C levels were reduced 44% from baseline and at week 78 a reduction of 38% was observed.[16] Although lomitapide is not FDA approved for patients other than those with HoFH, studies in other patients are being evaluated. A phase II RCT compared lomitapide monotherapy, ezetimibe monotherapy, and lomitapide plus ezetimibe in patients with LDL-C greater than 130 or 160 mg/dL, depending on risk factors. The lomitapide monotherapy dose was escalated over 12 weeks. LDL-C reduction of 20% to 22% was seen with ezetimibe alone, 19% to 30% with lomitapide alone, and 35% to 46% with combination therapy. Elevated transaminases and gastrointestinal effects were associated with lomitapide in both studies.[14,16] Increases in hepatic fat were also noted in the HoFH study; however, the clinical significance of this is currently unknown.[16] Another MTP inhibitor in development is SLx-4090. In mice fed a high-fat diet, LDL-C and triglycerides reductions were observed without elevations in transaminases or hepatic fat, making this a promising agent.[17] Findings from a phase II study evaluating the effects of SLx-4090 on LDL-C in combination with statin therapy have not been reported.[18]

Another class of interest for dyslipidemia treatment is the cholesteryl ester transfer protein (CETP) inhibitors. Although Pfizer halted studies of the first CETP inhibitor, torcetrapib, due to increased cardiovascular events and death associated with its use despite excellent increases in HDL in 2006, newer agents have demonstrated promising results with fewer AEs.[19] CETP is responsible for assisting the exchange of cholesteryl esters and triglycerides between HDL-C and apoB containing lipoprotein particles including LDL-C and VLDL-C.[19,20] Inhibition of CETP leads to increases in HDL-C, which may eventually lead to decreases in cardiovascular risk.[19]

Anacetrapib and evacetrapib are 2 CETP inhibitors currently in development, with anacetrapib being the more potent. Data from a double-blind RCT investigating the efficacy and safety of anacetrapib in patients with coronary heart disease (CHD) or at high risk for CHD with an LDL-C level of 50 to 100 mg/dL on a statin showed an almost 40% decrease in LDL-C and a 139% increase in HDL-C after 24 weeks of therapy.[21] Effects on blood pressure, electrolyte levels, or serum aldosterone levels were not detected, unlike with torcetrapib. Additionally, anacetrapib did not have the same rate of CV events seen with torcetrapib.[21] Two phase III studies are currently open to accrual, including the REVEAL study, which is evaluating anacetrapib's effect on major coronary events.[22,23] Evacetrapib is another CETP inhibitor under development. A phase II RCT demonstrated reductions of LDL-C by 11% to 14% and increases of HDL by 79% to 89% in patients taking evacetrapib 100 mg with either atorvastatin, simvastatin, or rosuvastatin.[24] As with anacetrapib, a phase III study is recruiting patients to determine its effect on cardiovascular outcomes.[25]

Weight

According to the American Heart Association, almost 155 million Americans are overweight or obese.[26] With this rising trend in the United States, the development of anti-obesity medications is important. Although dietary changes along with exercise are the mainstay of therapy, medications to be used as an adjunct to these lifestyle changes may be useful to some patients. Before the summer of 2012, when lorcaserin and topiramate/phentermine were approved, no new anti-obesity medications had been FDA approved since orlistat in 1998.[27] Currently, several other drugs are being evaluated for their weight loss effect. Not all of the agents under development are novel therapeutic classes. For example, one agent currently in phase III studies is a combination of a sustained-release formulation of the antidepressant bupropion with naltrexone.[28] Hypothalamus neurons known as pro-opiomelancortin (POMC) neurons send signals resulting in a anorexigenic ouput, making these neurons a potential target for weight loss drugs.[29] One proposed mechanism for bupropion-induced weight loss is due to the effect of dopamine and norepinephrine on POMC signaling. Reports of bupropion monotherapy for weight loss indicate therapy results in a modest weight loss with patients plateauing within several months.[29] Naltrexone, an opioid receptor antagonist, has demonstrated minimal weight loss when used alone. Investigators hypothesized that the addition of these 2 agents may result in a clinically significant weight loss effect because of the effect naltrexone may have on POMC signaling. Researchers have proposed that POMC stimulation results in the activation of a negative feedback system and they have demonstrated that opioids inhibit POMC neurons. The rationale for combining these 2 agents is that naltrexone would disrupt the feedback loop that occurs as a result of POMC activation.[29] Results of a phase II RCT comparing naltrexone/bupropion with placebo in patients with a BMI of 30 to 40 kg/m^2 showed participants had a 6% to 6.5% weight loss from baseline at 24 weeks (weight loss in intention-to-treat population was 3.5%-4.6%).The most common AE in patients receiving naltrexone/bupropion was nausea.[30] Data from a larger phase III study demonstrated results consistent with the previous trial. Weight was reduced by 5% to 6% in patients with a BMI of 27 to 45 kg/m^2 taking naltrexone/bupropion. A higher dose of naltrexone resulted in a greater reduction. Again, the most common AE was nausea.[31] Presently, 2 phase III studies with naltrexone/bupropion are ongoing, one of which is intended to provide insight regarding the effect of the drug on major adverse cardiovascular events.[32,33]

Bupropion in combination with zonisamide is another weight loss drug

THE AMERICAN JOURNAL OF MANAGED CARE

being developed. Zonisamide, an antiepileptic drug, is thought to further increase POMC stimulation. Results of a phase IIb study showed that at 24 weeks patients' weight decreased 9.9% from baseline compared with 1.7% with placebo. Almost 83% of patients decreased their weight by 5% of their baseline weight. Headache, insomnia, and nausea were the most commonly reported AEs.[34] According to the manufacturer's website, phase III studies are still in the planning stages.

Fumagillin is a potent and selective inhibitor of methionine aminopeptidase 2, which was isolated from the fungus aspergillus fumigatus.[35,36] Discovery of beloranib, a synthetic fumagillin analogue, began by investigating its anti-angiogenic effects in cancer. In animal studies subcutaneous or intravenous administration of low-dose beloranib reduced food intake, body weight, and adipocyte size.[36] Researchers conducted an RCT to determine the safety, tolerability, and pharmacology of beloranib in women with a BMI of 32 to 45 kg/m^2. Patients received 1 of 3 doses of beloranib or placebo as a twice-weekly intravenous infusion for 4 weeks. A dose-dependent weight loss was observed in patients receiving beloranib, with higher doses leading to a rapid and consistent weight loss of 1 kilogram per week. AEs observed in this study included nausea, dizziness, and migraines, with nausea being the most frequent. Nausea and infrequent episodes of vomiting had no effect on weight loss.[36] An ongoing phase II study will evaluate the safety and tolerability of twice-weekly beloranib injections by evaluating parameters such as AEs, physical exams, electrocardiograms, vital signs, and laboratory values.[37]

Blood Pressure

Elevated blood pressure, another component of cardiometabolic disease, has been associated with myocardial infarction, stroke, and heart failure. Despite the fact that almost 1 out of every 3 Americans over the age of 20 years has elevated blood pressure, novel agents to aid in treatment of this condition have been scarce.[38]

Neprilysin is a new pharmacologic target which has been identified to help in the development of new drugs to treat hypertension. When neprilysin is inhibited, this results in increased concentration of natriuretic peptides. Clinically significant reductions in blood pressure are not seen with only neprilysin inhibition, potentially due to the fact that neprilysin is responsible for the breakdown of certain vasoconstrictors, including angiotensin II.[39] By combining neprilysin inhibition with an inhibitor of the renin-angiotensin-aldosterone system, blood pressure–lowering effects may be more pronounced.[39] LCZ 696, a dual-acting angiotensin II receptor and neprilysin inhibitor (ARNI), is currently in phase III trials. A proof of concept study comparing varying doses of LCZ-696 with varying doses of the angiotensin receptor blocker valsartan in patients with mean diastolic blood pressure of 90 to 109 mm Hg over 8 weeks demonstrated significant reductions in blood pressure. The change in placebo-subtracted mean systolic and diastolic blood pressures was greater with LCZ-696 (systolic blood pressure: –6 to –12 mm Hg vs –5 to –6 mm Hg, diastolic blood pressure: –3 to –7 mm Hg vs –2 to –4 mm Hg). The results were statistically significant with the 2 highest doses of LCZ696.[39] Ongoing or proposed phase III studies with LCZ696 include studies evaluating the effects of neprilysin monotherapy in elderly patients, LCZ-696 compared with olmesartan, and LCZ696 plus amlodipine.[40]

Patients with cardiometabolic risk factors have annual healthcare costs $2000 higher than those without such risks.

Conclusion

Patients with cardiometabolic risk have increased healthcare utilization and costs compared with patients without similar risk. One US study estimated that patients with cardiometabolic risk factors have annual healthcare costs totaling $2000 more than those without such risks.[40] With cardiometabolic syndrome reaching epidemic proportions in the United States, the impact on overall healthcare costs is staggering. A large percentage of the costs comes from prescription drugs. While the mainstay of treatment remains lifestyle changes including diet and exercise, goals are often not met with these alone. Pharmacologic intervention remains a key approach to managing this cluster of related disease states. Focus on decreasing LDL, increasing HDL, weight loss, and lowering blood pressure and blood glucose are imperative mechanisms to decrease the risk factors that lead to CV disease. A number of novel agents have achieved significant results in decreasing cardiometabolic risk factors; however, it is too soon to determine the role they will play in clinical practice. While the costs of these agents are not yet known, several of them are injectable drugs and others are suggested in combination therapies. Both of these suggest a more expensive approach than what is currently available. Less expensive agents will likely remain the mainstay of treatment. The more costly agents should be reserved for those patients who cannot tolerate currently available medications, or for those who are unable to meet the goals with standard regimens. However, the impressive results seen in the treatment of dyslipidemia may have promise in the area of first-line treatment, with the main drawbacks being their route of administration and cost. Depending on the results of outcome trials, prescribers may choose these agents over oral medications in those patients with severe disease. **EBDM**

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versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

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

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA in nine clinical studies of INVOKANA *[see Clinical Studies (14.3) in full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA1C with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2); patients treated with INVOKANA 300 mg were more likely to experience increases in potassium *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Adverse Reactions]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Instructions: Instruct patients to read the Medication Guide before starting INVOKANA (canagliflozin) therapy and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also 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. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

Inform female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.

Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions such as urticaria and rash have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema, and to take no more drug until they have consulted prescribing physicians.

Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

Active ingredient made in Belgium

Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
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Titusville, NJ 08560

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Original Research

Clinical Outcomes Associated With Rates of Sulfonylurea Use Among Physicians

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Over the past 2 decades, the prevalence of diabetes mellitus has rapidly increased in the United States[1] and globally.[2] Estimates indicate that in 2010, nearly 19 million Americans had diagnosed diabetes, with 7 million more presumably undiagnosed.[3] Type 2 diabetes mellitus (T2DM) accounts for over 90% of new cases of diabetes in adults.[3] The wide range of available treatments has mitigated the impact of this growth[4] but has increased the complexity of T2DM management.

Metformin, a biguanide, is widely accepted and used as first-line treatment for T2DM.[4-6] Unlike many other agents, metformin causes neither acute hypoglycemia nor significant weight gain. Metformin use is usually only limited by gastrointestinal adverse events and is contraindicated in patients with impaired renal clearance. Although T2DM management guidelines do not name a preferred second-line agent,[4] sulfonylureas are prescribed as if they were the favored choice. After metformin, sulfonylureas are the second-most popular T2DM medication, prescribed to approximately one-third of patients.[7,8] Although sulfonylureas achieve glycemic control effectively,[9] their long-term effects on diabetes-related complications are not well established.[10] Widespread sulfonylurea use continues despite the availability of several newer T2DM agents, presumably because sulfonylureas are inexpensive and well established.[11-14]

With the passage of the 2010 Affordable Care Act (ACA), the Centers for Medicare & Medicaid Services (CMS) is required to report performance data on physicians billing Medicare through the Physician Quality Reporting System.[15] Currently, physicians voluntarily report performance data to CMS, but by 2015, the ACA will make it mandatory.[15] This system is intended to reward quality of care and reflects a movement toward physician assessments such as doctor report cards.[16] Because physician performance will be a key metric in determining US healthcare quality, it seems reasonable that physicians and stakeholders should have greater access to quality "physician-level" data to inform healthcare decisions. Specific performance measures are still being defined; the study presented here offers 1 possible measure.

In this retrospective, commercial, claims-based study, we examined the association between T2DM medication prescription patterns and physician performance. We measured physician performance using the occurrence of T2DM-related complications, including hypoglycemic and cardiovascular events, neuropathy, and lower-extremity, vision, and renal complications. We then determined whether T2DM medication prescription patterns were associated with physician performance rank. Our study takes the first steps toward assessing physician prescribing patterns as one simple and easily measurable tool for predicting physician performance. Moreover, we provide payers with a broader context to evaluate sulfonylureas and other T2DM therapies.

METHODS

Data

Humana is a large provider of commercial and Medicare Advantage health insurance plans. We examined patient claims data aggregated at the physician level using the 2007-2011 Humana database. To acquire the physician-level data, we first identified the patient cohorts that would be aggregated to the physician level by examining all commercially insured patient claims data and extracting incident and prevalent cohorts of T2DM patients. To reduce potential bias,[17] the incident cohort was used for base case analyses, while the prevalent cohort and 2 incident subcohorts were reserved for sensitivity analyses (reported in **eAppendix A**, www.ajmc.com). T2DM patients were identified as those with at least 1 claim with the *International Classification of Diseases, Ninth Revision* (*ICD*-9) code 250.x0 or 250.x2 and at least 1 claim for an anti-diabetic medication following the first observed claim with a T2DM diagnosis. Based on published results, these search criteria have a specificity range of 0.93 to 0.99 and sensitivity of 0.44 to 0.91.[18,19] Patients with claims for pregnancy (*ICD*-9 codes 630-79, V22.x–V24.x, V27.x, V29.x, V61.6, V61.7) were excluded during pregnancy and for 6 months thereafter. The cohort includes only working-age patients (aged 18-64 years).

For the prevalent cohort, the first-observed claim with a T2DM diagnosis provided the index date. Patients with less than 1 year of follow-up from the index date were excluded. The incident sample included all patients from the prevalent sample with at least 1 year of continuous enrollment prior to the index date, with no T2DM-related medical or pharmacy claims. We considered all available follow-up months of these patients. We also identified 2 incident subcohorts for sensitivity analyses: the second-line subcohort and the long-run therapy subcohort. In the second-line subcohort, we excluded patients from the incident sample if they did not require a second-line agent during the study period, and we considered all available follow-up months of the remaining patients. A *first-line therapy* was defined as the first anti-diabetic drug used after diagnosis. A second-line therapy was added to or replaced the first agent. For the long-run therapy subcohort, we selected follow-up months for incident patients in which patients used at least 1 drug class they also had used continuously for at least 6 months prior. The study selection criteria are detailed in **Figure 1**.

We collected patient characteristics including age and gender, and tracked monthly comorbidities, medication use, and complications. The Elixhauser Comorbidity Index (ECI) was calculated each month for each patient using comorbid diagnoses over the previous 12 months.[20,21]

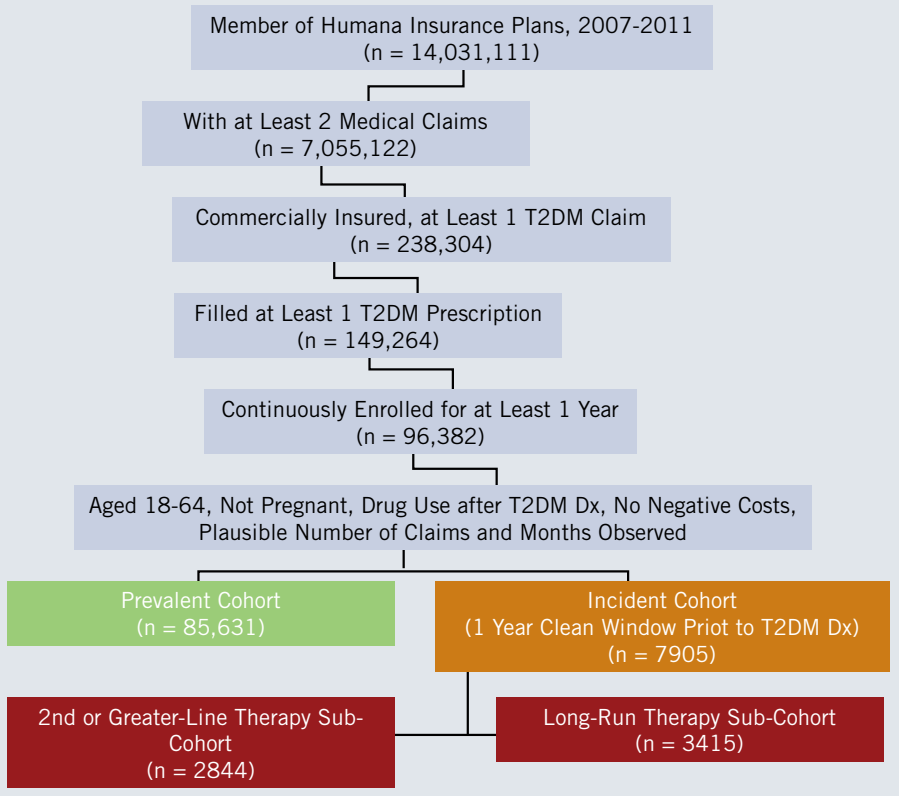
For each patient, we identified anti-diabetic drug use using the National Drug Code (NDC) Directory. We grouped T2DM medications by mechanistic class; specifically, biguanides (metformin), sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, insulins, and "other" (including alpha-glucosidase inhibitors, amylinomimetics, and meglitinides). For each patient, we identified T2DM-related adverse events (cardiovascular, lower-extremity, renal, ophthalmic, neurological, and severe hypoglycemic events) using *ICD*-9 and Current Procedural Terminology (CPT) codes (listed in **eAppendix B**, www.ajmc.com), consistent with previous literature.[22-27]

For each patient cohort (incident, prevalent, second-line, or long-run), we used physician identifiers from the pharmacy claims to link physicians prescribing T2DM medicines to each patient and compile an associated cohort of physicians. Once a patient received T2DM prescriptions from a provider, the patient was considered that provider's patient for the next 6 months. A patient receiving prescriptions from multiple providers was considered the patient of each. For each physician in each month, we calculated complication rates, average patient characteristics (age, sex, ECI), and average T2DM drug usage (fraction of patients using each class) among the physician's T2DM patients.

Statistical Analysis

After tabulating drug use and complication rates for the patient cohort, we created for each month in the study period a case-mix-adjusted measure of physician performance. Specifically, we calculated the fraction of a physician's patients experiencing any of the study complications in a given month. We then used a linear regression model to predict the monthly rate of any T2DM-related complication as a function of average age, gender, and ECI among patients in the practice in a given month, as well as a monthly time trend. This model provided a measure of physicians' performance as relative success at avoiding T2DM-related complications, after adjusting for their patients' age, sex, and comorbidities.

Figure 1. Study Cohort Selection



T2DM indicates type 2 diabetes mellitus.

After deriving this measure of physician performance, we sought to determine whether it was related to T2DM prescription patterns. To do this, we compared each physician's actual performance to the "risk-adjusted" performance predicted by patient characteristics alone (**Figure 2).** Those doctors with lower complication rates than predicted based on patient characteristics were considered "high performers," whereas those with higher complication rates than predicted were considered "low performers." We ranked physicians in each month based on their performance that month, and then sorted doctor-months into 10 ordered and equally sized groups (deciles). After establishing the 10-group ranking of physician performance, we analyzed whether the prescribing patterns in the month prior of highest performing doctors were different than those of the lowest performing doctors for each of the drug classes.

Finally, to quantify the impact of physicians' prescribing decisions, we expanded the previous regression model of physicians' T2DM complication rates on practice characteristics to include rates of use for each of the T2DM drug classes in the month prior. We used this model to predict the change in T2DM complications when switching from "low performer" (bottom decile) prescribing patterns to those of "high performers" (top decile). We performed sensitivity analyses on the prevalent, second-line, and long-run samples.

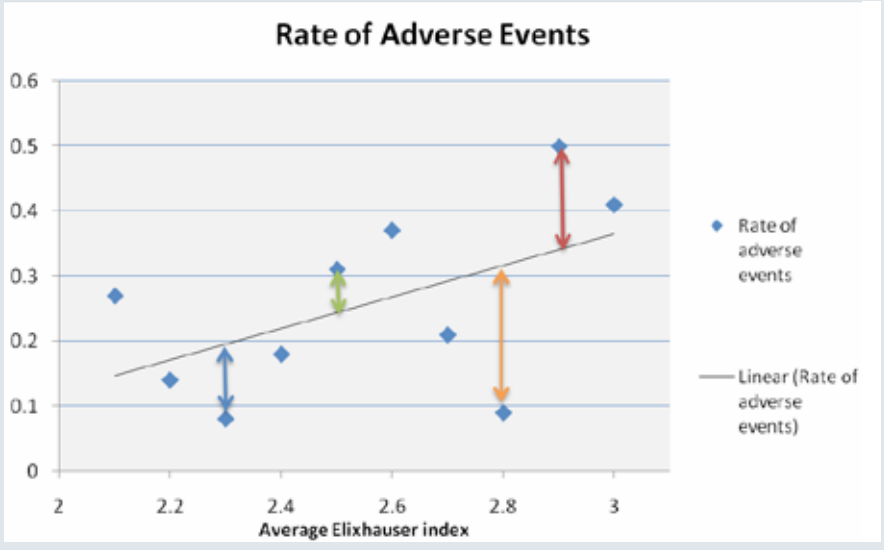
RESULTS

We identified an incident T2DM cohort of 7905 patients. Demographic descriptions are provided in **Table 1**. A majority of patients were men (n = 4418; 55.90%), and the most frequent age category was 46-55 years (n = 3155, 39.91%). The average age was 50.1 years.

Rates of T2DM drug use are summarized in **Table 2**. The biguanide (metformin) was used during 80,244 patient-months (37.46% of the total patient-months). Sulfonylureas were the second most commonly used (21,429 patient-months; 10.00%). TZDs were the third-most commonly used (8835; 4.12%). Every other drug class was filled less than 3% of the total patient-months. All insulin classes combined (bolus, basal, premixed) totaled 9709 patient-months (4.53%). Because metformin is widely accepted as the first-line T2DM medication,[4] these data suggest that sulfonylureas are the most commonly prescribed second-line agent in this cohort.

We compared baseline ECIs among all patients newly initiating each class of diabetes medication (**Table 3**). Patients newly initiating the biguanide had an average ECI of 2.38 in the year prior to initiation, the lowest score of any T2DM drug class. Sulfonylureas were prescribed to patients who had the second-fewest comorbidities at initiation (average ECI: 2.75). Patients who

Figure 2. Schematic Illustration of Doctor Performance Assessment



This figure presents a conceptual illustration of the measurement of case-mix–adjusted physician performance. The line represents the regression of complication rates at each physician's practice on the average Elixhauser index of the physician's patients, as well as other patient characteristics (omitted for ease of illustration). The assessment assumes that the adverse-event rate after T2DM medication initiation is proportional to comorbidities at the time of T2DM diagnosis. A physician with performance above or below the regression line has a higher or lower complication rate than others with similar case mix, respectively. The farther away the performance is from the regression line (increasing residual), the less it conforms to the expected performance for a given case mix (either better or worse).

received amylinomimetics had the most comorbidities, on average (4.00).

Rates of complications are summarized in **Table 4**. Cardiovascular complications were the most common, in 6378 patient-months (2.98% of the total patient-months), and neuropathy complications the least common, in 804 patient-months (0.38% of the total patient-months). Overall, 15,492 patient-months (7.23% of the total patient-months) involved any diabetes-related complication.

Table 1. Demographic Characteristics of Incident T2DM Patients

Patient Characteristic	Frequency N = 7905
Age, years, mean (SD)	50.1 (9.2)
Age category, n (%)	
18-25	95 (1.2)
26-35	501 (6.34)
36-45	1652 (20.90)
46-55	3155 (39.91)
56-64	2502 (31.65)
Gender, n (%)	
Men	4418 (55.90)
Women	3486 (44.10)

SD indicates standard deviation; T2DM, type 2 diabetes mellitus.

Among the incident cohort, we identified 10,457 distinct prescribing physicians. The average number of distinct prescribing physicians per incident T2DM patient was 1.7 (range, 1-9), whereas the average number of distinct incident T2DM patients (covered by Humana insurance) per prescribing physician was 1.3 (range, 1-18).

Figure 3 relates prescribing patterns to patient outcomes. Low-performing physicians (ie, those exhibiting higher complication rates for a given patient case-mix) were more likely than high-performing peers to prescribe metformin, sulfonylureas, and insulin. By contrast, high-performing physicians were more likely than peers to prescribe DPP-4 inhibitors, TZDs, GLP-1 agonists, or other classes of diabetes medications. The strongest correlation of drug use to performance was for DPP-4 inhibitors (R^2 = 0.1662), with increasing use of this drug class positively associated with fewer T2DM complications. Sulfonylureas (R^2 = 0.0857) and insulin (R^2 = 0.0166) were more commonly prescribed by low performers. The insulin relationship appeared nonlinear, with high prescription rates among both high and low performers, and lower rates among average performers.

After expanding the regression model to incorporate prescriptions of T2DM drug classes, we were able to predict the number of complications that would be avoided by moving from the prescribing patterns of bottom-decile to top-decile performers. In a population of 100,000 incident T2DM patients, such a change in prescribing patterns would amount to 924 avoided complications per year (95% CI, 597-1251).

DISCUSSION

Our analysis suggests that physicians prescribing sulfonylureas more frequently have a greater proportion of patients with long-term complications than those prescribing other second-line T2DM medications. After accounting for the prior-year health of patients, and other covariates such as age and gender, physicians prescribing sulfonylureas more frequently did worse than expected in preventing T2DM-related complications. Those using DPP-4 inhibitors at higher rates did better than expected, given the observed health of their patients. Physicians prescribing TZDs, GLP-1 agonists, or other newer agents at higher rates also performed better than expected. The amount of variance in prescribing a given drug class explained by physician performance is in the range of 1.7% to 16.6%—consistent with similar models using administrative claims data for various disease states including diabetes.[28-33]

Sulfonylureas are the most commonly prescribed T2DM medication after metformin. It is thus notable that physician tendencies to prescribe sulfonylureas more often are associated with poorer risk-adjusted outcomes. This finding is consistent with related findings in the clinical literature. Sulfonylurea or sulfonylurea-plus-metformin use may be associated with higher mortality rates than metformin alone.[34-37] Sulfonylureas are associated with a 4-fold increased risk for mild/moderate hypoglycemia compared with metformin alone.[9] When sulfonylureas were used as monotherapy, patients had higher blood pressure a year later than when they were prescribed metformin, an effect likely explained by increased body mass index (BMI) with sulfonylureas.[38] Likewise, adjusting for cardiovascular risk factors, the incidence of cardiovascular events such as myocardial infarction or stroke is higher in patients taking sulfonylureas versus metformin.[39,40] Compared with metformin, sulfonylurea use increased the risk of worsening glomerular filtration rate, progression to end-stage renal disease, and death.[41]

The American Diabetes Association (ADA) has estimated that the cost of diagnosed diabetes in 2012 was $245 billion; $176 billion for direct medical costs and $69 billion in reduced productivity.[42] The largest portion of this (43%) was due to inpatient care costs incurred due to diabetes complications. A greater portion of the total estimated cost of diabetes was spent on medications to treat the diabetes complications (18%) than on diabetes medications and supplies themselves (12%).[42] A 2007-2009 survey estimated that insulins and oral hypoglycemic

Table 2. Monthly Drug Use Among Incident T2DM Patients

T2DM Drug Class	Patient-Months in Use, Total (%)
Biguanides	80,244 (37.46)
Sulfonylureas	21,429 (10.00)
Thiazolidinediones	8835 (4.12)
Basal insulin	5917 (2.76)
DPP-4 inhibitors	4023 (1.88)
Bolus insulin	2806 (1.31)
GLP-1 agonists	1066 (0.50)
Premixed insulin	986 (0.46)
Meglitinides	493 (0.23)
Alpha-glucosidase inhibitors	44 (0.02)
Amylinomimetics	27 (0.01)
No drug use	115,694 (54.01)
Total patient-months	214,230

DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; T2DM, type 2 diabetes mellitus.

Table 3. Baseline Elixhauser Comorbidity Index Among T2DM Patients Initiating Drug Therapy

T2DM Drug Class	Elixhauser Comorbidity Index
Biguanides	2.38
Sulfonylureas	2.75
Thiazolidinediones	2.80
DPP-4 inhibitors	3.18
GLP-1 agonists	3.33
Basal insulin	3.48
Meglitinides	3.63
Premixed insulin	3.76
Bolus insulin	3.93
Alpha-glucosidase inhibitors	3.95
Amylinomimetics	4.00

Scores calculated using the Elixhauser Comorbidity Index.[20,21]
DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

agents were the second- and fourth most-common causes of emergency admission, together accounting for 1 in 4 emergent medication-related admissions.[43] Given the high cost of diabetes complications, future research should investigate whether the cost savings of using an inexpensive drug class (sulfonylureas) actually represents an overall cost savings when complication rates are high and may outweigh initial savings.

Our study did have limitations. The relationship between physician prescription patterns and patient complications may be confounded by the patients' diabetes severity level and other health characteristics. Although we accounted for age, sex, and comorbidities in our analyses, data limitations prevented us from controlling for a fuller set of characteristics. Because sulfonylureas are a common therapy and patients initiating them are relatively healthy **(Table 3)**, we find it noteworthy that a strong positive association between sulfonylurea prescription and T2DM complications remains. Further research is needed to shed light on this issue.

As ours and other studies have shown, sulfonylureas are a popular second-line agent in the treatment of T2DM. However, our physician-level study design suggests a potential pitfall associated with their use. Physicians who prescribe sulfonylureas more frequently than their peers have patients with higher complication rates than would be expected from their age, sex, and preexisting comorbidities. This could be due to the properties of the drugs themselves; it could also be due to the skills and characteristics of the physicians who choose to use these drugs more often, or the unmeasured characteristics of their patients. Further investigation is needed to assess whether physician prescribing choices accurately predict patient outcomes, and whether they can serve as an additional metric of quality in today's changing healthcare reimbursement landscape. **EBDM**

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Authorship Information: Concept and design (KB, KFB, DL, AS, JTS, NT, DG); acquisition of data (KFB, DL, AS, DG); analysis and interpretation of data (KB, KFB, DL, AS, JTS, NT, DG); drafting of the manuscript (KB, JTS, NT); critical revision of the manuscript for important intellectual content (KB, DL, AS, JTS, NT, DG); statistical analysis (KB, AS, JTS); provision of study materials or patients (KFB, NT); obtaining funding (KFB, DL, NT, DG); administrative, technical, or logistic support (KB, KFB, JTS); and supervision (KB, KFB, DL, JTS, DG).
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Table 4. Average Complication Rates Among Incident T2DM Patients

Complication Type, n (%)	Rate per Patient per Month
Cardiovascular disease	6378 (2.98)
Lower-extremity complications	4577 (2.14)
Ophthalmic disease	1019 (0.48)
Renal disease	4586 (2.14)
Neuropathy	804 (0.38)
Hypoglycemic emergencies	857 (0.40)
Any diabetes-related complication	15,492 (7.23)

T2DM indicates type 2 diabetes mellitus.
Based on *International Classification of Diseases, Ninth Revision* and Current Procedural Terminology codes. (For specific codes, see eAppendix B, www.ajmc.com.) Cardiovascular events include myocardial infarction, congestive heart failure, ischemic heart disease, and stroke. Lower-extremity complications include arterial occlusion, Charcot foot, claudication, gangrene, lymphangitis, osteomyelitis, paresthesia, ulcer, and amputation. Ophthalmic disease includes diabetic retinopathy, diabetic macular edema, microaneurysms, and blindness. Renal disease includes chronic renal failure, diabetic nephropathy, end-stage renal disease, and proteinuria.

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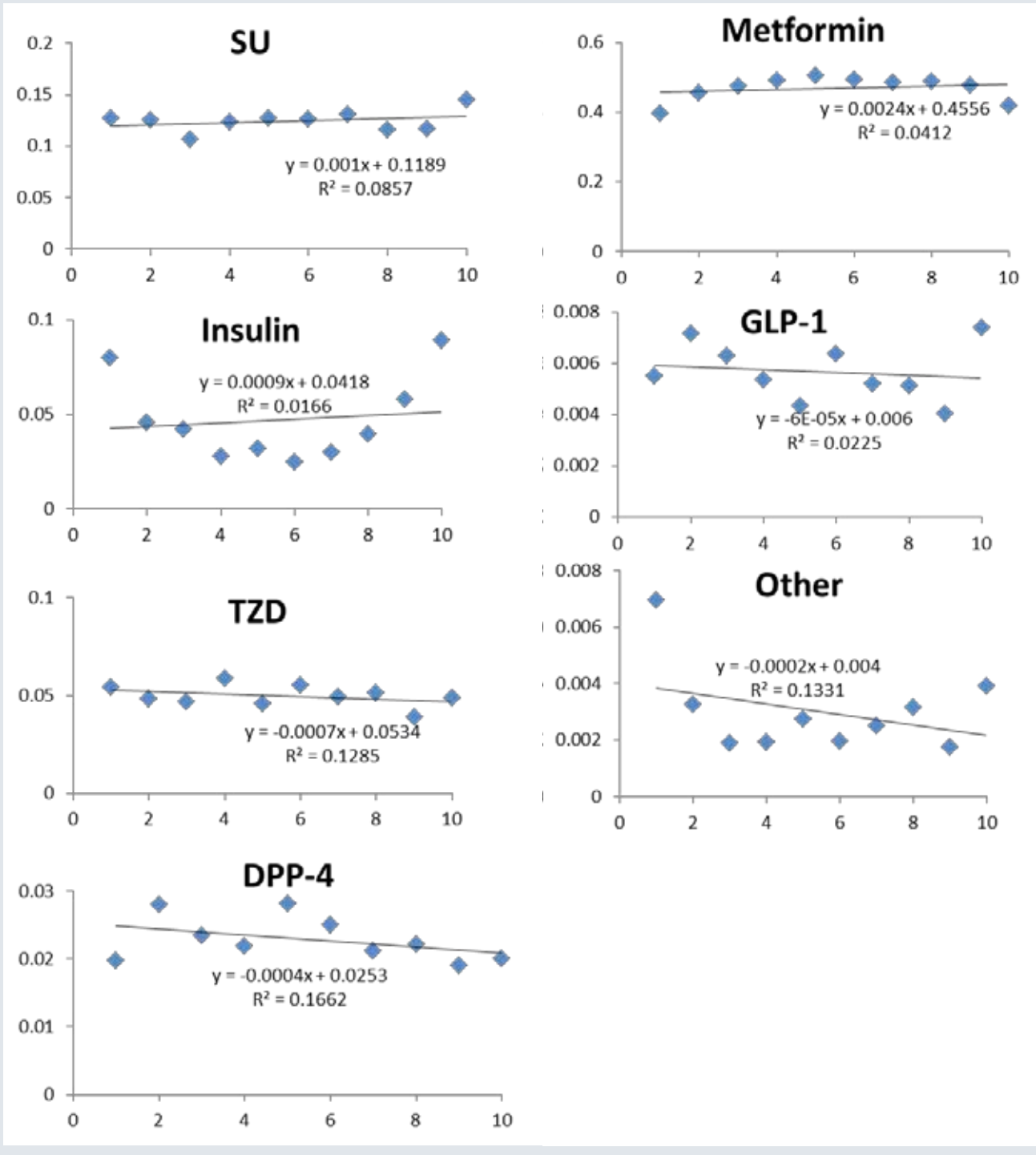
Figure 3. Drug Use Patterns Among the High- and Low-Performing Doctors of Incident Patients



DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SU, sulfonylurea; TZD, thiazolidinedione.
The units on the abscissa correspond to the 10 physician performance deciles; 1 = highest performing; 10 = lowest performing. The ordinate shows the fraction of patients in a physician's practice using the given drug class. Each diamond represents the average rate of drug class prescribing among physicians in the given performance decile.

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Diabetes Apps
(continued from cover)

A published clinical trial from *Diabetes Care* showed that patients with type 2 diabetes who received behavioral mobile coaching through the use of tracking medications, caloric intake, glycemic levels, and other management information, compared with usual care without mobile coaching, were more likely to experience greater decreases in glycated hemoglobin (A1C). The difference between groups was 1.2% over a 12-month period (P <.001).[3] While ongoing research is being conducted to determine the impact of electronic documentation on clinical outcomes, the importance of getting patients involved is likely to improve decision support among health care providers.

The table (**Table**) shows frequently used apps and key features contained within each app to aid in the management of diabetes. These apps were selected based on their ability to perform specific functions for diabetes care, were given high ratings from users, and are free for public use. Various paid apps are also available, although patients may choose to demo 1 or more free versions first to help them discover their preferred user interface and become acquainted with electronic documentation. Before recommending these apps, healthcare professionals should become familiar with the terminology and functionality unique to these applications, as detailed below.

Mobile apps for managing diabetes focus on three areas: glucose control, medication logs, and food tracking.

There are 3 major focus areas of the mobile apps for diabetes:

Glucose Control

All of the mobile apps have a method for tracking glucose lab values. The apps allow users to specify the time and date of the glucose value and select the relationship to meals (eg, before or after breakfast) as well as physical activity (eg, before or after physical activity). Another possible function is the ability for each patient to enter specific glucose levels in which they feel they are most likely to experience symptoms of hypo or hyperglycemia. Some apps may allow entry of custom glucose goals, contain graphs of glucose trends over a certain time period, and record A1C levels.

Medication Log

Another key feature of some of these apps is their ability to track medication compliance. Patients can log the time of day that insulin injections, oral medications, and other dosage forms were administered. For quick entry, some apps also have a built-in preset dropdown selection for various types of insulin. A note field is included in most of the medication logs, which could be helpful for patients wishing to document any additional information beyond medication administration.

Food Log

Patients with diabetes are counseled on the importance of a well-balanced diet to achieve adequate glucose control. Some apps provide easy tracking of how many calories, carbohydrates, and other nutrients are consumed in any given meal. Others have a built-in food database for patients to simply select which foods they ate at any particular time of day. A selection can be made from an alphabetical list of foods, which then yields an approximate carbohydrate value based on the nutrition label. This can subsequently be added to the food log. Alternatively, apps may simply allow for patients to arbitrarily enter foods consumed and estimate carbohydrate grams for eachmeal.

Miscellaneous Features

Other functions contained in some apps are the ability to enter notes in various fields, export data (eg, Excel) for future retrieval, e-mail reports to healthcare providers, and track weight and blood pressure parameters. Patients who decide to upgrade to paid apps may find additional tools such as medication and appointment reminders, broader dropdown selections, educational notes, insulin calculators, and other specialized features. **EBDM**

Author Disclosures: The authors (K-AT, NE) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Table: Free Mobile Apps for Managing Diabetes

Features	Diabetes App Lite	Diabetes Companion	Diabetes Manager	Glucose Buddy	OnTrack Diabetes	WaveSense Diabetes Manager
A1C estimator				✓[a]	✓	
Calorie counter	✓			✓[b]		
Carbohydrate log	✓	✓		✓		✓
Exercise log	✓	✓[c]		✓	✓	✓[c]
Food database	✓	✓[d]				
Food log	✓	✓		✓	✓	✓
Glucose log	✓	✓	✓	✓	✓	✓
Glucose log category	✓	✓		✓	✓	✓
Glucose graph		✓	✓	✓	✓	✓
Insulin dose log	✓	✓	✓	✓	✓	✓
Medication log	✓			✓	✓	
Weight log	✓				✓	
E-mail reports		✓	✓	✓	✓	✓
Note field	✓	✓		✓	✓	✓
Color coding		✓		✓		✓
Compatibility	iPhone, iPod touch, iPad	iPhone, iPod touch, iPad	Windows Phone	iPhone, iPod touch, iPad, Android	Android, BlackBerry	iPhone, iPod touch, iPad
Special Features	• Water intake log • Build recipe in food database • BMI tracker • Ability to budget daily carbohydrate allowance	• Online videos	• Diabetes news • Customizable target ranges	• Sync to online account • Set reminders for glucose readings	• Blood pressure log • Set reminders for glucose readings	• Online videos • Customizable target ranges
Average User Rating	**4**	**2.5**	**4.5**	**4.5**	**4.5**	**3.5**

A1C indicates glycated hemoglobin; BMI, body mass index.
a = Available on Android, but web version only for Apple devices.
b = Must install and integrate CalorieTrack (free app).
c = Information is a scroll down option in note field, not a separate log.
d = Look up recipes for patients with diabetes.
Ratings (out of 5) = generated using average ratings as viewed on the available mobile device app stores.

Interview With Javier Morales, MD

(continued from cover)

sociated with tight glycemic control, which was revealed by the 2008 Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[1]

The glycated hemoglobin (A1C) levels used as a target in the ACCORD trial were very aggressive—an A1C level of 6% or lower, compared with the ADA's recommendation of 7.0% or AACE's (American Association of Clinical Endocrinologists) standard of less than or equal to 6.5%.

Also, ACCORD investigators attempted to reduce A1C levels rapidly, and found that patients with known coronary disease, or who had experienced a previous coronary event, were more likely to suffer a new coronary event or to die as a result of aggressive titration and possibly hypoglycemia. In 2009, a position paper was published in *Diabetes Care,* which suggested using judgment in liberalizing glycemic control of patients with multiple comorbidities and advancing age.[2] That was extrapolated even further in the 2012 revised American Diabetes Association guidelines. The ADA has a beautiful diagram looking at various parameters, such as the age of the patient, comorbidities, longevity, and whether clinicians should be treating more or less aggressively.

> *"The take-home message is, you need to exercise judgment, but if the patient is younger, more aggressive glycemic control will be better."*
>
> **—Javier Morales, MD**

Liberalizing diabetes control doesn't mean that an A1C of 8.5% is acceptable. I think that's where there will be a lot of confusion in the medical community: A relatively high A1C level may be deemed more acceptable to some, which is counter to the conservative, longstanding recommendations.

The take-home message is, you need to exercise judgment, but if the patient is younger, more aggressive glycemic control will be better, because it will minimize the risk of microvascular complications in patients with T2DM. In older patients, the benefits of long-term, tight glycemic control, for the sake of minimizing microvascular complications, are fewer, and the risks associated with hypoglycemia may be greater.

EBDM: **To what extent were the rigid glycemic control protocols in the ACCORD trial attempted by ordinary practitioners?**

Morales: My understanding is that most clinicians are aiming for A1C levels of less than 7.0%. I think they (and their patients) are comfortable with the risk of hypoglycemia in this range. Below this, the hypoglycemic risk may be too great for them.

EBDM: **Have changes in insulin formulations also affected the ability to, and comfort with, achieving tight glycemic control?**

Morales: Absolutely! We learned from the Diabetes Control and Complications Trial (DCCT) that there is a hyperbolic-shaped hypoglycemic risk as you get closer to target A1C levels. However, at the time the DCCT investigators studied this risk, older insulin formulations were used—NPH and regular insulin; the insulin analogues were not yet available. I believe that with the insulin analogues now available, the hyperbolic response with hypoglycemia is much less pronounced, allowing us to achieve tighter control with fewer hypoglycemic events. The rationale for this is that insulin analogues are much more predictable, or have much less variability. AACE recommends the use of insulin analogues over human insulin, because of the variability factor. Even newer insulin formulations that are currently in development offer even less variability, thus enabling patients to get safely to target a little sooner.

EBDM: **Let's talk specifically about the newer-versus-older basal insulins in patients with T2DM. Insulin degludec may be the newest, ultra long-acting basal, but its approval was delayed by the FDA, pending more detailed evaluation of its cardiovascular risks. If we assume that the FDA approves it over the next 18 months or so, what do you view will be its advantages?**

Morales: The first ultra long-acting insulins approved were lente and ultra lente, which are no longer available. The problem with those insulins was significant stacking, which is the continued effect of the previously injected insulin dose superimposed on the increasing effect of the newly injected insulin dose, and high variability in effect. Clinicians started using intermediate-acting insulin instead. Today, the long-acting basal market is dominated by insulin detemir and insulin glargine, and these represent significant strides with respect to basal insulin management. In the T2DM population, differences in variability between insulin detimir and insulin glargine are not clinically significant.

Most recently, insulin degludec was approved by the FDA's Advisory Committee. It is different because it creates a "string-of-pearls effect" in which insulin hexamers break off into monomers and subsequently release into circulation, resulting in a flat glucose infusion rate profile and a relatively steady basal insulin plasma concentration after only two doses, which is very impressive.[1] Keep in mind, there have not been any head-to-head studies looking at the amount of variability among insulin detimir, insulin glargine, and insulin degludec.

Investigators did test the glycemic control associated with glargine and degludec head-to-head in basal-bolus treatment (treat to target), as well as the use of these insulins as add-on therapy to orals.[1] The ability to reach target glycemic levels was high in both groups, indicating noninferiority between the insulin studied, allowing a look at other variables and parameters, and significantly less hypoglycemia was seen in the insulin degludec group—on the order of 36% fewer nocturnal hypoglycemic episodes in those patients having received degludec as and on therapy with orals medications.

EBDM: **Wouldn't you expect that insulin degludec, with a longer half-life than insulin glargine, be subject to greater hypoglycemic risk?**

Morales: No, because its method of subcutaneous collection and release of insulin degludec is much more predictable and less variable. Remember, in terms of insulin-related hypoglycemia risk, the 1 major factor that affects the rate of hypoglycemia will be the rate of variability in the insulin's pharmacodynamic activity.

EBDM: **Do you think the introduction of insulin degludec (when and if that occurs) will significantly alter the utilization of other basal insulins?**

Morales: Yes and no. If you're trying to reach a fasting glucose of 70 mg/dL, you may be able to get there with less hypoglycemic risk with insulin degludec rather than insulin glargine. The reality is that there will be challenges based on insurance coverage and availability. Furthermore, if liberal control is what the practitioner and patient are aiming for, then there may be little difference between degludec and the currently available basal insulins.

EBDM: **New GLP-1 and DPP-4 agents are seemingly being introduced every year or so, and now it appears that the SGLT-2 inhibitors will be joining the party. What is your view on what these new drugs have to offer?**

Morales: The incretins are here to stay; they're a no-brainer. They offer minimal hypoglycemia risk unless utilized in combination with secretagogues. While incretins seem to have an effect on glucose-dependent insulin secretion out of the beta cell, they do have a suppressive effect on glucagon release out of the alpha cell. Other currently available agents don't offer anything with respect to glucagon release, or even the weight loss that is offered with GLP-1 receptor agonists.

The DPP-4 inhibitors' claim to fame really is more based on glucagon suppression than it is on insulin secretion, in a glucose-dependent fashion. That's why the A1C reductions we see with these agents is only about 0.6 percentage points, and slightly higher in treatment-naïve patients. The challenge we face as practitioners is trying to control postmeal glycemic excursions without increasing the risk of hypoglycemia.

Often, practitioners will prescribe a DPP-4 rather than a GLP-1, because they believe that a DPP-4 is more or less an oral version of a GLP-1. That's not really the case; however, the prescriber's mind-set is influenced by the problem with getting patients to go on injectable therapy. Even though the GLP-1s offer better A1C reduction, systolic blood pressure control, and weight loss than the DPP-4 inhibitors, clinicians will often reach for a DPP-4 rather than a GLP-1. The prescribing community needs to realize that incretin resistance also exists in the T2DM population. In one study, restoring GLP-1 levels to physiologic levels offered very little with respect to insulin secretion in T2DM patients. However, in a different study, a dose of 3 times physiologic levels restored insulin secretion in these patients to near normal levels. Furthermore, it also had a positive effect on first-phase insulin release. Unfortunately, the DPP-4 inhibitors only restore endogenous GLP-1 to

THE AMERICAN JOURNAL OF MANAGED CARE

physiologic levels.

EBDM: **In your own practice, are you shifting more of these patients away from other oral antidiabetic drug classes to the GLP-1s and DPP-4s?**

Morales: The best answer to this question is that there will be something for everyone. It depends on what comorbidities you may be treating, who you're treating, where you are in terms of hemoglobin A1C, the duration of that patient's diabetes, and his or her likely response to therapy, followed by insurance limitations.

There's data suggesting that the more agents a patient is currently taking...the longer we wait to further intensify their therapy.

The other thing that must be factored into the decision is the sustainability of A1C control. Not only do you want to achieve A1C control but the goal would be to sustain it. The thiazolidiones (TZDs) are the only class of agents found to provide sustained hemoglobin A1C levels. The ADOPT trial showed that a TZD (rosiglitazone) provided A1C control that lasted 5 years.[2] While data are not yet available, I am optimistic that the incretin agents will demonstrate similar sustainable results over the course of 5 years and beyond.

For a new patient with T2DM who is treatment naïve, the standard of care is that you start with metformin, if no contraindication exists, along with exercise and diet modification. But is this enough? We learned from UKPDS and ADOPT trials that sustainability with metformin therapy was not achieved, yet we did see some weight stabilization in those who were obese, and noted cardiovascular protection in the UK PDS trial. Should we be treating with combination therapy sooner, specifically for the sake of beta-cell preservation? I tend to embrace a more synergistic approach to control rather than a stepwise approach. Taking a stepwise approach ends up not working in the long run. In fact, there are data suggesting that the more agents a patient is currently taking to manage their diabetes, the longer we wait to further intensify their therapy. This leads to the progression of underlying microvascular disease, which is what we are trying to avoid by intensive therapy to begin with. As a result, I tend to embrace a more synergistic approach when managing my patients rather than a stepwise approach.

EBDM: **Do you think that as clinicians become more comfortable with prescribing the incretins, they will become a de facto third tier of therapy or will they be substituted for another drug class early on?**

Morales: Safety always resonates in the medical community. Achieving fasting plasma glucose control safely and minimizing postprandial excursion without hypoglycemia is our goal. The incretins are helpful in this regard. The short-acting GLP-1 agents offer prandial control, while the long-acting GLP-1 agents offer prandial and fasting control. In those using insulin, the combination of these agents shows extremely encouraging results. In fact, there is a new long-acting GLP-1 agent that was studied in combination with basal insulin, versus a short acting insulin analogue looking at prandial control. The GLP-1 agent did better. The DPP-4 agents also result in less insulin need, which may be useful for those taking basal insulin in combination with other oral agents. The newest anti-diabetes drug class, the SGLT-2s, will probably factor into this decision. They are a very interesting class, because they offer a weight-loss benefit. And they do improve glycemic control significantly, but this will have to be weighed against a small but higher risk of urogenital tract infections (relative to placebo).

EBDM: **How do you think payers will react to the SGLT-2s? Will they put them on formulary after the usual waiting period, or will they take an extended wait-and-see attitude?**

Morales: Of course, there will be a waiting period, just like for any other drug that comes along. The insurance companies need to establish whether there's a need for these new agents in the marketplace. I think taking into consideration safety and the financial implications of hypoglycemic reactions, namely on emergency department visits, additional phone calls, additional glucose test strips that may be utilized, the insurance companies would err on the side of safety. Like any new kid to the marketplace, there will be a delay before they're actually embraced and approved by payers.

EBDM: **How do you think prescribers will react to the SGLT-2s?**

Morales: When it comes to prescribers, there will always be those early adopters who embrace the newest technologies right away, and there will be those who will wait. I tend to be an early adopter and embrace newer technologies. I have an advantage being involved academically and knowing the clinical data.

EBDM: **It sounds to me that, in the future, prescribers will be taking a more mix-and-match approach to individual patients, with clinicians using all the different drug classes in their arsenal, and that we may be moving away from a standardized step-therapy approach that is promoted in today's type 2 diabetes treatment guidelines.**

Morales: People have their target glycemic level in mind. It's just a matter of how they will reach that target. We can't forget that it's about safety as well as efficacy. You want to be able to achieve your target glycemic level in a reasonable time frame, but you want the patient to get there safely. The question is, how many practitioners will feel comfortable with utilizing all of these different tools in order to allow their patients to get to their proposed target, and how quickly they will embrace the new agents that will soon be available? While we've learned more about the natural history of T2DM progression, other organs involved in glycemic management besides the pancreas, the management of T2DM continues evolving with newer, safer, and more reliable agents. We owe it to our patients to use these tools to their fullest potential. **EBDM**

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Commentary

Comparative Effectiveness Research

(continued from cover)

of complex comorbidities and complications. Understanding the clinical nuances of when and to whom services render the greatest benefit requires more research. The type of research that addresses this issue is commonly labeled comparative effectiveness research (CER)—although CER by other names has been around for years. Recognizing the need for stronger evidence-based practice, the ACA invested in greater CER by establishing the Patient-Centered Outcomes Research Institute (PCORI) which will commission independent CER.[1] Starting in 2011 and moving forward, PCORI will act as a funding source for independent research institutions to conduct CER-related research and will synthesize these findings and make them available to the public.

CER is especially important in diabetes care because of the pervasiveness and multifaceted nature of the disease. Diabetes is one of the nation's most prevalent chronic conditions, with over 8% of the US population living with the disease.[2] In part due to its chronic nature and because of several widely accepted high-value treatments, the management of diabetes has become a widespread benchmark of quality. For example, most standard quality measurement systems, including the Healthcare Effectiveness Data and Information Set and most pay-for-performance systems, include a series of diabetes-related measures. These include clinical services (eg, eye and foot exams) as well as drug management for hyperglycemia, hypertension, and hypercholesterolemia. Due in part to the effectiveness of treatment and disease management as compared with non-treatment, the US Preventive Services Task Force recommended diabetes screening as a high-value preventive service and in turn the ACA has mandated payers to provide diabetes screening without patient cost-sharing. While there is broad consensus that several treatments are clinically effective, there is still great opportunity for CER to elucidate the optimal combination of treatments for each patient population.

There is also an opportunity to gain much more value for the money we spend on the treatment of diabetes. The American Diabetes Association estimated around $116 billion in medical

expenditures associated with treating diabetes in 2007, and perhaps as much as $58 billion in reduced worker productivity.[3] Pharmaceuticals represent about 12% of total healthcare expenditure, but could potentially have a sizable spillover effect on inpatient and emergency department visits, as well as substantially reduce the risk of costly complications such as cardiovascular complications, amputation, and end-stage renal disease.[4,5] In addition, despite the proven value of early and aggressive treatment, diabetes-related medications generally share the same problematic adherence patterns seen in prescription use. While the drivers of adherence are many and complex, benefit design (and, specifically, member cost-sharing levels) has been tied to significant changes in patient behavior regardless of the clinical value of the medication.[6] Thus payers, and especially pharmacy benefit managers (PBMs) who play a pivotal role in managing formularies, have an opportunity to use CER to improve the value of spending on patients with diabetes.

The promise of CER will be realized only if patients, providers, insurers, and other stakeholders act on the findings. This can be done in several ways including supply side initiatives (Value-Based Purchasing [VBP]) and demand side initiatives (Value Based Insurance Design [VBID]). In the case of pharmaceuticals, VBID entails using CER to guide formulary placement. Specifically, the alignment of clinical knowledge and financial incentives can promote an efficient delivery system. The status quo generally has failed to align quality improvement and cost containment initiatives. In fact, in some instances, these actually compete with each other, contributing directly to inefficiency.[7] In most situations, formulary placement and patient copayment amounts are based on the cost of a drug within its sub-class of therapeutically similar alternatives (eg, dipeptidyl peptidase-4 [DPP-4] X vs DPP-4 Y), not the value of the drug relative to treatments for other disease areas (eg, a DPP-4 vs an acne therapy), relative to alternative therapies for the same disease (eg, a DPP-4 X vs a thiazolidinedione [TZD] or a glucagon-like peptide-1), or relative to varying uses of the product (eg, a DPP-4 as first-line or fourth-line therapy). As a result, patients face the same out-of-pocket costs for all drugs on a given tier regardless of the relative therapeutic value provided.

A more thoughtful approach would be to use CER to guide and target formulary placement more efficiently and effectively. The idea of using CER to guide formulary placement is an important component of the principles of VBID. The basic VBID premise is to align patients' out-of-pocket costs with the value (defined as benefit relative to cost) of health services. This approach to designing benefit plans recognizes that different health services have different levels of value. By reducing barriers to high-value treatments (through lower costs to patients) and discouraging low-value treatments (through higher costs to patients), these plans can achieve improved health outcomes at any level of healthcare expenditure. This can be incorporated at 3 levels of sophistication—across disease areas (eg, diabetes vs acne), within disease areas (eg, DPP-4s vs TZDs), and within drug (eg, DPP-4 use first vs fourth line, or for patient x vs patient y, etc). The broadest application, and the easiest to implement and communicate, would be the entire class of diabetes medications placed on a tier that incentivizes (or avoids dis-incentivizing) adherence. A more refined approach would reserve preferred tier placement for diabetes treatment sub-classes. Finally, and both most coherent and most difficult, individual medications or services could be tiered according to specific needs or actions of a patient (ie, according to indication, place in therapy, program participation, etc). However, such an alignment of incentives is only possible in the setting of improved clinical evidence. Driven by CER, VBID represents a clinically sensitive, fiscally responsible approach that advocates keeping patient out-of-pocket payments low on high-value services and raising them on services of no or marginal clinical value.

Benefit design, specifically cost-sharing, has been tied to significant changes in patient behavior, regardless of the clinical value of the medication.

Such an alignment of clinical and economic incentives facilitates patients making appropriate choices both because evidence suggests that formulary positioning can influence patient decisions on what product to use (ie, formulary positioning can drive positive change to more high-value use and not just lower-cost use), and to mitigate against the unintended consequence of increasingly higher cost sharing. When faced with higher costs, patients often make poor clinical decisions, which in fact could, in some cases, lead to greater overall costs.[8-10] By using incentives to encourage the use of high-value services and discourage the use of low-value ones, VBID has the potential to achieve marked increases in the efficiency of the healthcare system. More health can be achieved at any level of spending.

In the case of diabetes, VBID has already been implemented in several large corporations. Recognizing the clinical and potentially cost-saving value of diabetes medication, both Pitney Bowes and Marriott International, Inc, implemented a VBID program that reduced the copayments for diabetes treatment and a handful of other chronic conditions.[11] The University of Michigan took a related approach that focused solely on diabetes treatment, lowering copayments and coinsurance for diabetes-related office visits and medication.[12] These initiatives all identified the clinical and potential economic benefit of incentives-based disease management among diabetics and lowered out-of-pocket expenses across the board. This broad-stroke approach is a first, blunt step to aligning copayments with value. Refining the approach by adjusting formularies between classes of diabetes-related therapies to incentivize high-value use may prove effective at guiding patients to more efficient treatments. Going yet another step, there is potential for incorporating clinical nuance that differentiates the value of individual medications based on the profile or behavior of a specific patient.

Regardless of sophistication in application—across disease, within disease, across drug (the current formulary focus), or within drug—more coherent formulary development will also need to address the consequences of some CER-influenced decisions. From one extreme to the other—whether all diabetes products are placed in a low tier because they are categorically considered to be of high value or whether only specific high-value uses of diabetes products are in a low tier—removing the primary role of formularies today (ie, tier differentiation based on cost for products with similar profiles) will greatly increase healthcare costs. This does not imply that the application of greater CER-facilitated sophisticated tier differentiation will come at the expense of cost management. For example, a low-cost diabetes product with high CER defined health benefit could be placed in a low copay tier, while a high-cost product with a similar CER health benefit could be placed in a high copay tier despite high clinical utility. In these scenarios, however, it is crucial to recognize that incentives must balance the role of cost-sharing in unit cost control and behavior change with the potential to discourage the high-value treatment. Patients facing higher copays for drugs they are currently using may opt to take no medications instead of switching drugs. Payers and PBMs will need to evaluate the value of cost containment across products, with the potential trade-offs in high value product use—particularly as cost sharing rises over time.

In incorporating CER into formularies a few basic principles should be considered. First, CER should take a broad perspective. Notably, many CER studies will not compare one drug against another, but instead will compare one broad treatment strategy (eg, drug treatment) against another broad strategy (eg, surgery). In fact the Institute of Medicine CER priority list generally focused on these broad strategies as opposed to drug versus drug studies.[13] Formulary placement should not be based only on drug versus drug information. For example, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial demonstrated that outcomes from stents were no better than those with medical management.[14] Yet, use of drugs did not change with these findings, suggesting the need for improvement in the transition from research to implementation.

Second, CER should incorporate all outcomes, not just those directly related to the service. This includes the possible reduction in use of other services associated with greater medication adherence or disease management. While CER may not include economic outcomes (existing rules prohibit PCORI-funded CER from examining cost), assessment of value, and thus formulary placement, does require some attention to cost. Previous work has demonstrated that the spending offset associated with better drug adherence may be significant. For instance, a Medicare policy change in California in 2002 that raised office visit and drug copayments by $5 to $20 was associated with a 6% greater likelihood of being hospitalized.[5] This greater expenditure on inpatient hospitalization offset around 20% of the

THE AMERICAN JOURNAL OF MANAGED CARE

savings associated with increased patient cost sharing. Similar research on the impact of Medicare Part D shows that increased medication coverage was associated with fewer hospitalizations,[15] and that for groups with the greatest change in benefit generosity, the increased expenditure on drugs was totally offset by a reduction in medical expenditure.[16] While these studies provide useful analysis for several types of medical expenditure, offsets should be even broader to include non-medical components such as productivity in the workplace. Better chronic care management may reduce disability and absenteeism. Currently, data limitations often prevent such analysis. Advocating greater investment in building such data is crucial to the next stages of CER and cost containment.

A third principle to guide CER-related formulary placement is recognition that the goal of the healthcare system is not to save money, but to improve health. Similarly, CER-guided formulary placement should aim to encourage high-value uses, which will often increase drug and even total expenditures. That said, the system must be fiscally sustainable, which is a far cry from today's reality. CER can help achieve financial sustainability by allowing targeting of populations that will benefit from specific products and by identifying low-value services. Strategies that finance favorable formulary placement of high value by spreading the cost across other services can improve the efficiency of the system.

Formulary design traditionally has focused on saving money through cost-sharing tiers that differentiate medications with therapeutically similar effects. Over time, the number of tiers and associated cost-sharing amounts have increased, and there is reason for concern that these growing costs may increasingly impact patient adherence and adversely affect health outcomes. Historically, the decisions have been made largely on the basis of the cost of medications across a range of therapeutically similar alternatives, without much consideration of the clinical benefit achieved in one disease area versus another, one disease sub-class versus another, or even in one patient type versus another. Without a strong investment in CER that enables greater sophistication in formulary structure, patients are more likely to face "across the board" increases in cost sharing. That trend makes it increasingly likely that the unintended consequences of discouraging appropriate management of chronic disease will grow. In the case of diabetes—partially due to the fact that, in many cases, the management of hyperglycemia, hypertension, and hypercholesterolemia require more than 1 medication—suboptimal management (ie, lack of adherence due to cost-related issues) may lead to expensive complications. CER can provide the knowledge base necessary to add clinical nuance to formularies—possibly by distinguishing across disease states (eg, diabetes versus acne), within disease drug classes (eg, insulin vs DPP-4s), and within drug uses (eg, Januvia first versus fourth line)—in addition to distinguishing across a class of similar products (eg, generic vs brand versus non-preferred brand), which has been the main focus of formulary management to date. Cost-containment efforts that rely on an improved evidence base are probably preferable to current efforts to drive all practice toward those of the lowest cost. Thus, formularies of the future can use findings from CER to better target, not limit, care. **EBDM**

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Studies have shown that the spending offset associated with better drug adherence may by significant. Raising Medicare costs was associated with a 6% greater likelihood of hospitalization.

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Keynote Session: How Does Oncology Fit Into the New ACO World?
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- Oncology Practice in the Era of PCMHs and ACOs: Square Pegs or Round Holes?
- Where Do Major Cancer Centers Fit In: Focus on the Impact of Clinical Studies in Accountable Care
- Evaluating Episodes of Care in Oncology: The Impact of Payment Reform on Data Collection and Reporting
- Making the Pegs Fit: Implementation Case Studies

The Role of Companion Diagnostics in Targeted Treatments

- Where Do They Fit In? A Focus on OncoType DX
- Clinical Utility vs Cost vs Quality: Quantifying the Value of Personalization
- Diagnostic Preview: A Look Into the Future (Abstract Presentation)

Patient-Centered Oncology Care

- The Role of Consumerism in Deliverability of Care
- Implications of Healthcare Reform: "No" Will Be Heard
- End-of-Life Care: A Delicate Balance of Cost and Quality

Pharma/Payer Collaboration: A Focus on the Future (Panel Discussion)

- Where Does HEOR Fit in the Oncology Model? What Data Do Payers Want? If Pharma Provides, Will They Use It?
- Value-Based Pricing: The Role of Outcomes Data in Pricing Models
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Appendix A. Sensitivity Analyses

In addition to the base case analyses of the incident cohort, three additional samples were analyzed as sensitivity analyses: the prevalent cohort and the second- or greater-line therapy and long-run therapy incident subcohorts. Demographic characteristics of these samples, as well as the incident cohort (for comparison), are presented in **Table A1**. As expected, prevalent patients were slightly older than incident patients (average age, 51.1 and 50.1 years, respectively), and incident subcohort patients were similar to those of the broader incident cohort.

Drug use among the three additional samples, as well as the incident cohort (for comparison) is presented in **Table A2**. Biguanides and sulfonylureas were the most commonly used drug classes in all samples. In the prevalent sample, the biguanide was used during 1,076,312 patient-months in the sample (41.07% of the total patient-months), followed by sulfonylureas, which were prescribed during 526,113 patient-months (20.08%). Biguanide prescriptions were filled 37.46% of the total patient-months in the incident sample (41.73% for incident second-line and 74.64% for incident long-run subcohorts), whereas sulfonylureas were the second most commonly used (10%; 26.04%; 21.89%). As would be expected based on their having a more advanced state of disease, prevalent cohort members used all T2DM therapy classes at higher rates than their incident counterparts. Incident second-line and long-run subcohort members used more of all drug classes than the typical incident patient, although this increase in drug use was smaller among biguanide and sulfonylureas and larger among the newer therapy classes.

Table A3 presents complication rates for the three additional samples, as well as the incident cohort (for comparison). As expected, complication rates were higher among prevalent than incident patients. Among the members of the incident subcohorts, second-line therapy users had higher rates of all study complications except cardiovascular, for which the long-run therapy users had a higher rate. Compared to the broader incident cohort, members of these subcohorts had higher rates of cardiovascular (3.04% of the total patient-months in incident second-line and 3.27% in incident long-run vs 2.98% in broader incident), renal (2.70%; 2.17%; 2.14%), and ophthalmic complications (0.89%; 0.64%; 0.48%), but long-run therapy users had lower rates of lower extremity complications (1.99% vs 2.14% in broader incident) and severe hypoglycemia (0.25%; 0.40%).

Table A1. Demographic Characteristics of T2DM Patients

Patient Characteristic	Prevalent Frequency, n (%) N = 85,631		Incident Frequency, n (%) N = 7905		Incident 2nd-Line Frequency, n (%) N = 2844		Incident Long-Run Frequency, n (%) N = 3415	
Age, mean (SD)	51.1 (9.2)		50.1 (9.2)		48.9 (9.3)		51.3 (8.5)	
Age category								
18-25	1081	1.26%	95	1.20%	44	1.55%	24	0.7%
26-35	4775	5.58%	501	6.34%	212	7.45%	146	4.28%
36-45	15,195	17.74%	1652	20.90%	667	23.45%	616	18.04%
46-55	32,187	37.59%	3155	39.91%	1173	41.24%	1410	41.29%
56-65	32,393	37.83%	2502	31.65%	748	26.30%	1219	35.70%
Gender								
Male	45,794	53.48%	4418	55.90%	1697	59.69%	1976	57.86%
Female	39,829	46.52%	3486	44.10%	1146	40.31%	1439	42.14%

Table A2. Monthly Drug Use among T2DM Patients

Rate per Patient per Month	Prevalent Frequency, n (%)		Incident Frequency, n (%)		Incident 2nd-Line Frequency, n (%)		Incident Long-Run Frequency, n (%)	
Sulfonylureas	526,113	20.08%	21,429	10.00%	13,573	26.04%	5792	21.89%
DPP-4 Inhibitors	85,528	3.26%	4023	1.88%	3185	6.11%	1191	4.50%
Biguanides	1,076,312	41.07%	80,244	37.46%	21,746	41.73%	19,746	74.64%
Thiazolidinediones	356,222	13.59%	8835	4.12%	5188	9.95%	2289	8.65%
GLP-1 Agonists	53,140	2.03%	1066	0.50%	871	1.67%	282	1.07%
Bolus Insulin	148,320	5.66%	2806	1.31%	2110	4.05%	414	1.57%
Basal Insulin	239,974	9.16%	5917	2.76%	4554	8.74%	1236	4.67%
Premixed Insulin	56,853	2.17%	986	0.46%	609	1.17%	152	0.58%
Meglitinides	15,919	0.61%	493	0.23%	382	0.73%	144	0.54%
Alpha-Glucosidase Inhibitors	2970	0.11%	44	0.02%	21	0.04%	2	0.01%
Amylinomimetics	3052	0.12%	27	0.01%	27	0.05%	7	0.03%
Total patient-months	2,620,604		214,230		52,118		26,455	

Note: DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.

Table A3. Average Complication Rates among T2DM Patients

Rate per Patient per Month	Prevalent Frequency, n (%)		Incident Frequency, n (%)		Incident 2nd-Line Frequency, n (%)		Incident Long-Run Frequency, n (%)	
Cardiovascular disease	101,057	3.86%	6378	2.98%	1585	3.04%	866	3.27%
Lower-extremity complications	75,156	2.87%	4577	2.14%	1449	2.78%	527	1.99%
Ophthalmic disease	30,995	1.18%	1019	0.48%	463	0.89%	170	0.64%
Renal disease	89,423	3.41%	4586	2.14%	1408	2.70%	575	2.17%
Neuropathy	19,763	0.75%	804	0.38%	358	0.69%	101	0.38%
Hypoglycemic emergencies	17,925	0.68%	857	0.40%	306	0.59%	65	0.25%

Note: Based on ICD-9 and CPT codes. (For specific codes see Appendix B.) Cardiovascular events include myocardial infarction, congestive heart failure, ischemic heart disease, and stroke. Lower-extremity complications include arterial occlusion, Charcot foot, claudication, gangrene, lymphangitis, osteomyelitis, paresthesia, ulcer, and amputation. Ophthalmic disease includes diabetic retinopathy, diabetic macular edema, microaneurysms, and blindness. Renal disease includes chronic renal failure, diabetic nephropathy, end-stage renal disease, and proteinuria.

Using the same methods as for the incident sample (base case) analyses, we ranked doctor-months by the difference in predicted versus actual performance and compared prescribing patterns across the high and low performers. The results of these analyses are presented in **Figures A1** (prevalent cohort), **A2** (second-line incident subcohort), and **A3** (long-run therapy incident subcohort).

Among physicians of prevalent T2DM patients, the relationship between prescribing choices and doctor performance differed from that observed in

Figure A1. Drug Use Patterns Among the High and Low Performing Doctors of Prevalent T2DM Patients

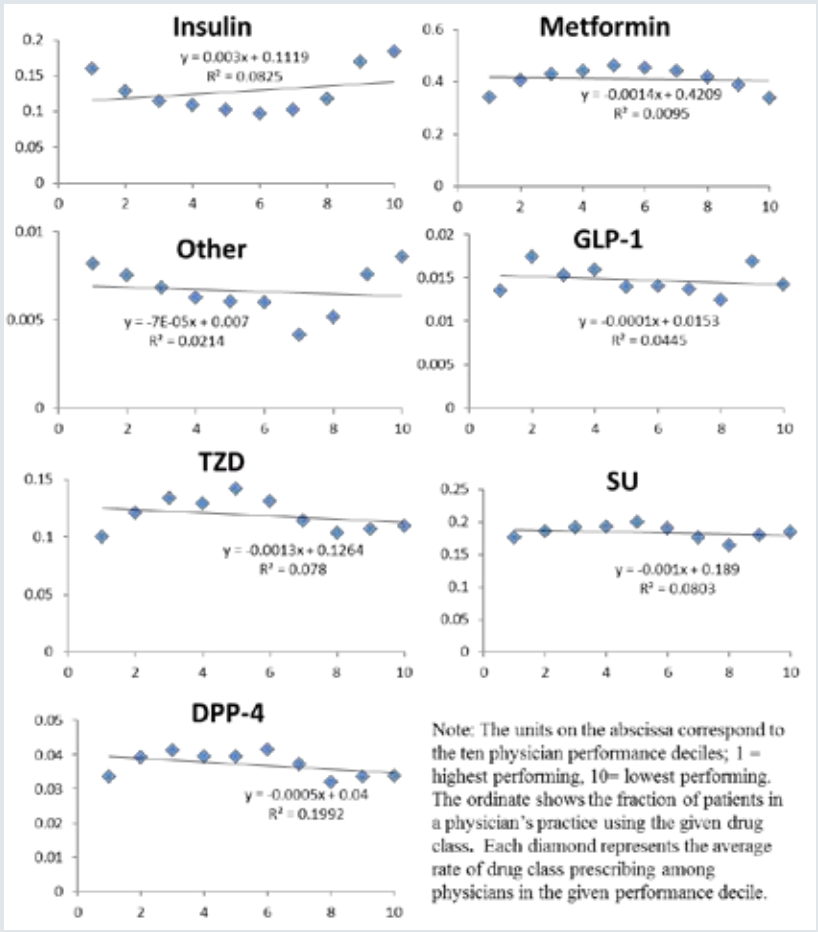
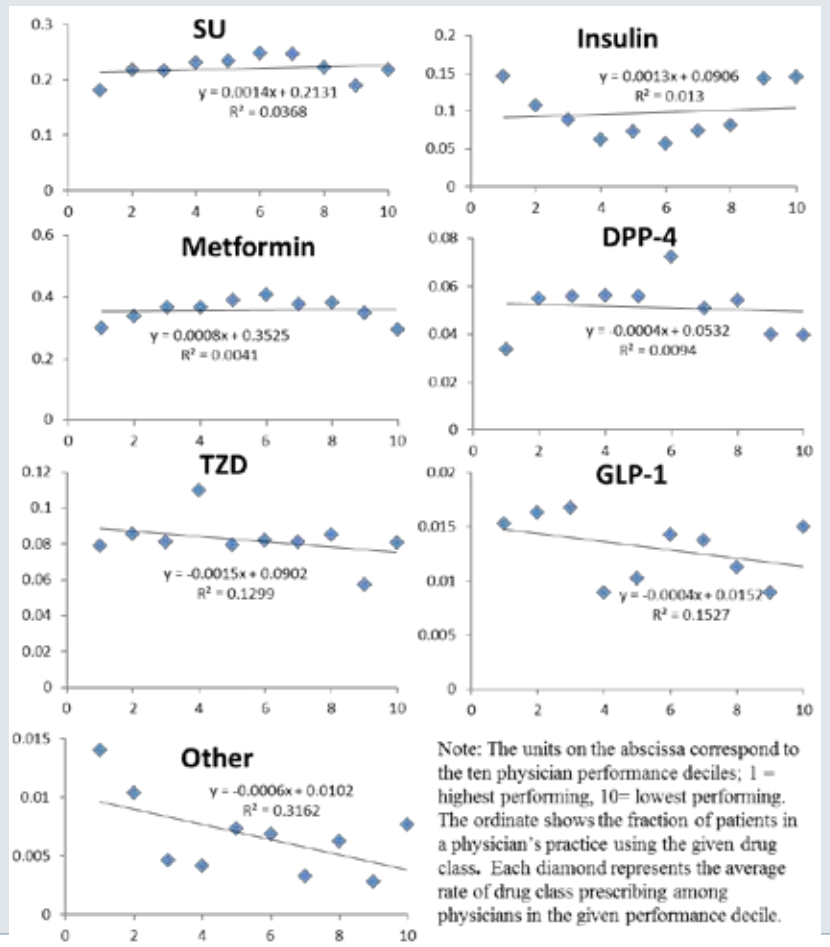


Figure A2. Drug Use Patterns Among the High and Low Performing Doctors of Incident T2DM Patients on 2nd- or Greater-Line Therapy

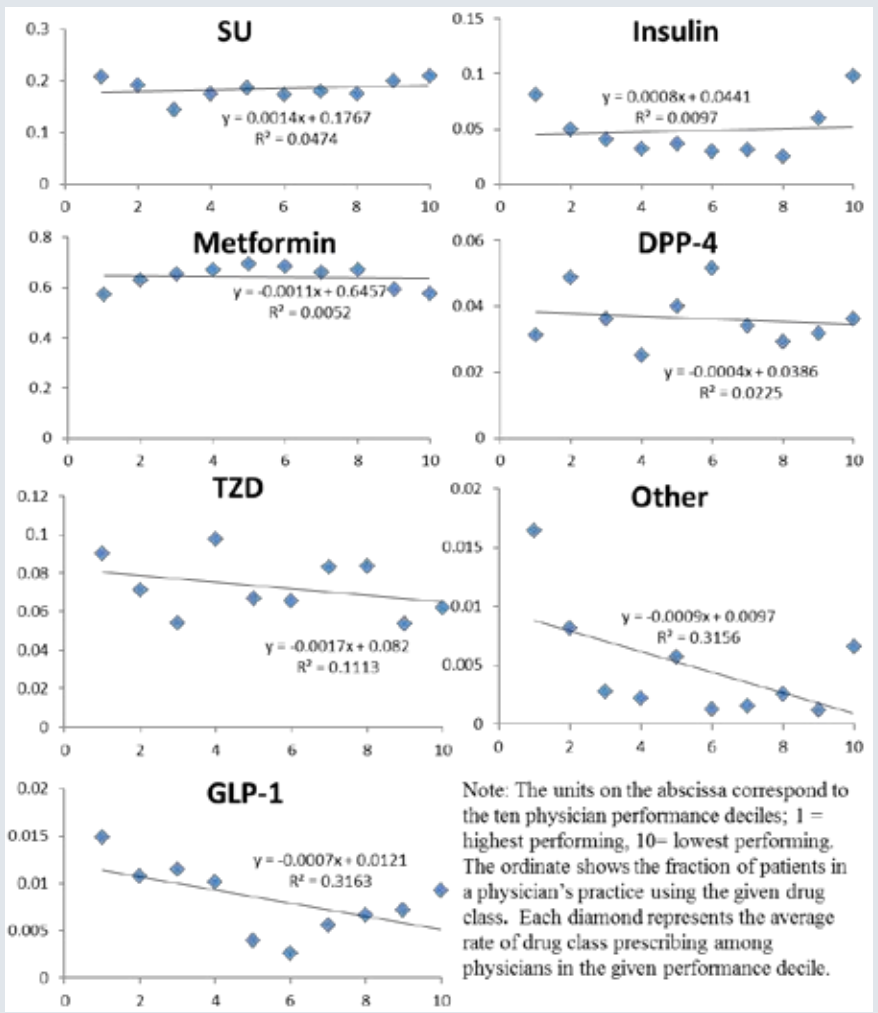


the incident patients. In particular, the only drug class that was used more heavily by lower-performing physicians than by higher performers was insulin. All other classes were prescribed at lower rates among low performers than among high performers. However, the heterogeneity in unobserved severity of illness among prevalent patients would likely be great, making it difficult to infer the meaning of this result.

Among physicians of the second-line and long-run therapy subcohorts, the relationship between prescribing choices and doctor performance was similar to that observed in the base case incident cohort. Sulfonylureas and insulin were more heavily prescribed among low performers than among high performers, although the relationship for insulin appeared nonlinear, with high use among low and high performers and lower use among average performers. DPP-4, TZD, GLP-1 and the "other" drug classes were prescribed at lower rates among the low performers than among the high performers.

For each of the three additional samples, we quantified the number of complications that would be avoided by moving from the prescribing patterns of the lowest-decile-performing physicians to those of the highest-decile performers. Among 100,000 prevalent T2DM patients, this would amount to 1519 avoided complications per year (95% CI, 1395-1643). Among 100,000 incident T2DM patients using second- or greater-line therapy, such a change in prescribing patterns would be associated with 633 avoided complications per year (95% CI, 0-1267). Finally, among 100,000 incident T2DM patients with long-run use of therapy, such a change would amount to 1354 avoided complications per year (95% CI, –106-2814).

Figure A3. Drug Use Patterns Among the High- and Low-Performing Doctors of Incident T2DM Patients on Long-Run Therapy



Appendix B. List of Diabetic Complication ICD-9 Codes

Diabetic Complications	ICD-9 and CPT Codes
Cardiovascular disease	429.7x (Certain sequelae of myocardial infarction not elsewhere classified) 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 428.0, 428.1, 428.9, 428.2x, 428.3x, 428.4x (Congestive heart failure) 410.xx (Myocardial infarction) 433.xx, 434.xx (Occlusion or stenosis of cerebral arteries) 412 (Old myocardial infarction) 411.xx (Other acute and sub-acute forms of ischemic heart disease) 414.xx (Other forms of chronic ischemic heart disease) 430.xx, 431.xx, 432.xx, 436.xx (Stroke) 435.xx (Transient ischemic attack) CPT Codes 33510-33523, 33533-33536 (CABG) 92980-92982, 92984-92996 (PCI)
Lower-extremity complications	440.20-440.24, 440.29, 440.4 (Arterial occlusion) 713.5 (Charcot foot) 443.9, 440.21, 440.22 (Claudication) 040.0, 250.7, 440.2x, 785.4 (Gangrene) 457.2 (Lymphangitis) 730.0x, 730.1x, 730.2x, 730.97 (Osteomyelitis) 782 (Paresthesia) 250.70, 250.72 (Peripheral circulatory disorder) 440.23, 707.xx (Ulcer) ICD-9 Procedure Codes 84.1x (Amputation) CPT Codes 27290, 27590-27592, 27594, 27596, 27880-27882, 27884, 27886, 27888, 27889, 28800, 28805, 28810, 28820, 28825 (Amputation) 11000, 11042 (Debridement)
Ophthalmic disease	362.01 (Background diabetic retinopathy) 362.07 (Diabetic macular edema) 362.01 (Diabetic retinal microaneurysms) 369.xx (Low visual acuity or blindness) 362.04 (Mild nonproliferative diabetic retinopathy) 362.05 (Moderate proliferative diabetic retinopathy) 362.03 (Nonproliferative diabetic retinopathy NOS) 362.29 (Other nonproliferative diabetic retinopathy) 362.02 (Proliferative diabetic retinopathy) 361.0x, 361.2x, 361.3x, 361.8x, 361.9x, 362.30-362.34, 362.4x, 362.81, 379.23 (Proliferative retinopathy) 362.06 (Severe nonproliferative diabetic retinopathy) 379.23 (Vitreous hemorrhage) CPT Codes 67208, 67210, 67218, 67228 (Low visual acuity or blindness)
Renal disease	403.xx, 404.xx, 585, 586, 593.9 (Chronic renal failure) 583.81 (Diabetic nephropathy) V42.0, V45.1, V56.0, V56.8, 585.5, 585.6 (End-stage renal disease) 581.8x (Nephrotic syndrome) 791.xx (Proteinuria) ICD-9 Procedure Codes 39.27, 39.42, 39.43, 39.49, 39.50, 39.53, 39.93-39.95, 54.98, 55.6x (End-stage renal disease) CPT Codes 50360, 50365, 90918-90925, 90935, 90937, 90940, 90989, 90993, 90999, 93990 (End-stage renal disease)
Neuropathy	355.8 (Mononeuropathy of lower limb) 357.2 (Polyneuropathy in diabetes) 357.4 (Polyneuropathy in diseases classified elsewhere)
Glycemic emergencies	250.1 (Diabetic ketoacidosis) 250.20, 250.22 (Hyperosmolar syndrome) 250.3 (Diabetes with other coma) 250.8* (Diabetes with other specified manifestations) 251.0, 251.1, 251.2 (Hypoglycemia) 270.3 (Disturbances of branched-chain amino-acid metabolism) 962.3 (Poisoning by insulins and antidiabetic agents) * If either of the diagnosis codes 259.8x,272.7x,681.xx,682.xx,686.9x,707.1x,707.2x,707.8x,707.9x,709.3x,730.0x, 730.1x,730.2x or 731.8x appear on the same claim as 250.8, then that claim is disqualified as a hypoglycemia claim