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Evidence-Based Diabetes Management

THE PREVENTION ISSUE

Policy Commentary

Prevention of Type 2 Diabetes Requires BOTH Intensive Lifestyle Interventions and Population-Wide Approaches

ANN ALBRIGHT, PHD, RD

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the CDC.

More than 29 million people in the United States have diabetes, up from the previous estimate of 26 million in 2010, according to the latest report from the CDC. Another 86 million adults—more than 1 in 3—have prediabetes, meaning that their blood glucose levels are higher than normal but not high enough to classify them as having type 2 diabetes mellitus (T2DM).[1] Only about 10% of these people know they have prediabetes.[2] The costs for treating and managing diabetes continue to rise. Besides the actual daily demands of the condition, the American Diabetes Association's estimate is $245 billion annually in direct and indirect costs.[3]

We cannot afford to continue on this path. It is imperative that we make meaningful strides in preventing diabetes as we continue to improve treatment and look for cures.

HOW DID WE GET HERE?

The growing epidemic of T2DM has strong roots in modern culture. People are busy, stressed, and eat on the run. Many people live in neighborhoods that promote poor health, and

(continued on page SP238)

Community Strategies

Building Community-Clinical Linkages to Address the Diabetes Epidemic

BRENDA SCHMIDT, MS, MBA

With the right support, community providers can offer an effective approach to promoting population health and preventing chronic disease.

This time of intense change in the US health system offers an opportunity to make a concerted effort to improve the health of the population. Population health holds the promise of better care for patients, better health for the population, and lower healthcare costs by addressing health disparities and reversing the escalating epidemic of chronic diseases, such as obesity, diabetes, and cardiovascular disease.

Despite the fact that the term population health denotes community, many approaches to population health do not fully integrate community-based providers as an adjunct to primary care. An article published in the *Journal for Public Health Management and Practice*, "Population-Based Health Principles in Medical and Public Health Practice," states that traditional medical education, research, and practice have focused on the care of the individual.[1] Shifting the emphasis to the care of populations has raised awareness among academic medical centers, integrated delivery systems, and managed care organizations of the value of embracing population-based health principles, which can have a greater effect on health and wellness. The authors outlined the following 5 principles in the article:

- a community perspective

(continued on page SP240)

Pharma Feature

Real-World Evidence Mounts for Rivaroxaban

ANDREW SMITH

Studies Offer Insights for Patients With AF and T2DM, With More Results to Come

A steady stream of follow-up research suggests that the novel oral anticoagulant (NOAC) rivaroxaban will fulfill the promise it showed in trials and provide a superior combination of stroke prevention, safety, and convenience for patients with nonvalvular atrial fibrillation (AF) and a wide variety of comorbidities, such as type 2 diabetes mellitus (T2DM).

Subgroup analysis indicates that rivaroxaban compares as well to warfarin (in terms of both safety and efficacy) in small patient segments as it compares to the older drug in AF patients as a whole.[1]

Studies of clinical usage, moreover, have demonstrated an advantage that trials did not: the relative ease of rivaroxaban use, compared with warfarin, reduces the percentage of patients who give up on anticoagulation therapy and use less effective stroke prevention strategies.[2]

These same studies have raised some issues that should be noted by physicians who treat both AF and T2DM. Overall, however, they contain good news for the many patients who have both conditions. (Estimates of comorbidity vary, but research suggests that T2DM may double a patient's odds of developing AF,[3] and that about 17% of patients with AF have diabetes.[4])

"Substudies have shown that the beneficial effects of rivaroxaban are consistent with the results of the overall study, irrespective of the history of previous stroke or transient ischemic

(continued on page SP241)

DETECTING DIABETES SP222

PHOTO CREDIT: PAULA BURCH-CELENTANO

A recent study in *Diabetes Care* found that states with Medicaid expansion in 2014 saw a 23% increase in the number of diagnoses of type 2 diabetes mellitus among enrollees, while states without expansion saw almost no increase.

Also in this issue...

PREVENTING KETOACIDOSIS

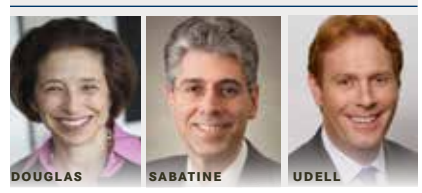
Risk factors associated with diabetic ketoacidosis (DKA) generally cannot be altered. But better education and awareness, along with efforts to identify those most likely to have an episode, could help reduce DKA incidence (**SP224**).

NEW INSULINS

The FDA recently approved 2 new insulin therapies, Toujeo and Afrezza, but labeling restrictions prevent marketing of some important benefits that were seen in clinical trials (**SP226**).

AMERICAN COLLEGE OF CARDIOLOGY

ACC 2015



The 64th Scientific Sessions featured important findings about heart scans and more results about a PCSK9 inhibitor that could reach the market this summer. Another study showed hospital mortality rates in low-income areas for heart attack patients are not tied to the quality of care, which in many cases is superior to hospitals elsewhere. For full coverage, see **SP230**-**SP237**.

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*Data on file. Based on TRx data sourced from IMS NPA and NSP databases, weekly data through 3/2/15.
†Approval from the Food and Drug Administration (FDA) was granted in March 2013.
Reference: 1. Data on file. Janssen Pharmaceuticals, Inc., Titusville, NJ.

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SP230 *The PROMISE study, presented at the 64th Scientfic Sessions of the American College of Cardiology (ACC), found that patients receiving computed tomography angiography fared about as well as those who had functional testing for coronary artery disease. Full coverage of ACC 2015 appears in SP230-237.*

Finding and Preventing Diabetes, and Keeping Complications at Bay

"The Prevention Issue" of *Evidence-Based Diabetes Management* covers many aspects of preventing and dealing with chronic illness. Clearly, the most important public health goal is to identify those persons with prediabetes and help them halt disease progression to type 2 diabetes mellitus (T2DM), as Ann Albright, PhD, RD, of the CDC outlines in her commentary in the current issue. Making the National Diabetes Prevention Program widely available will require buy-in from stakeholders across the healthcare spectrum, including employers and payers, and it's a worthwhile investment.

In diabetes care, however, this is just the start of "prevention." Some already have T2DM and have not been diagnosed. As we predicted a year ago—and report in this issue—the uneven implementation of Medicaid expansion means many cases will be caught earlier, before serious complications arise, while others will be missed. In the realm of type 1 diabetes (T1DM), the challenge of preventing ketoacidosis has both clinical and managed care implications. Patients who suffer these episodes experience significant and possibly life-threatening health effects, and the cost of care for each event is far too high, making prevention a priority for health plans and accountable care organizations. On the research front, work with very young patients who have a family history of T1DM suggests that high doses of insulin may offer a way to prevent onset of the disease. For those living with either type of diabetes or with related cardiovascular issues, such as atrial fibrillation, the pharmaceutical world continues to improve treatment options.

Stories in this issue review the real-world evidence of the effectiveness of rivaroxaban, for which studies involving patients with T2DM continue. We also learn in this issue about new insulin options, including an inhaled version that is receiving strong reviews from T1DM patients. Finally, we bring you full coverage from the recent Scientific Sessions of the American College of Cardiology, including studies on successful interventions for T2DM, the importance of payment reform in cardiology, and a report on the effectiveness of evolocumab, one of the new class of cholesterol fighters, the PCSK9 inhibitors, that face summer deadlines for FDA action. These are exciting times in diabetes care, as patients and providers are gaining many new options for treating both the disease and its many complications.

As always, we appreciate your readership. Please look for updates on our live meetings and our conference coverage at www.ajmc.com.

Sincerely,

Brian Haug
President, *The American Journal of Managed Care*

EDITORIAL MISSION

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

Evidence-Based
Diabetes Management

EDITORIAL BOARD

An option for type 2 diabetes therapy starts here

Trulicity™ is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use: Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. Has not been studied in patients with a history of pancreatitis; consider another antidiabetic therapy. Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. Not a substitute for insulin. Has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. Not for patients with pre-existing severe gastrointestinal disease. Has not been studied in combination with basal insulin.

Select Important Safety Information

WARNING: RISK OF THYROID C-CELL TUMORS

In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies.

Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with Trulicity. Counsel regarding the risk factors and symptoms of thyroid tumors.

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

once weekly

trulicity™

(dulaglutide) injection

0.75 mg/0.5 mL, 1.5 mg/0.5 mL

Trulicity™: An option for your plan members

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

*In clinical trials, the range of A1C reduction from baseline was 0.7% to 1.6% for the 0.75 mg dose and 0.8% to 1.6% for the 1.5 mg dose.[1]

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

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

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

Limitations of Use: Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. Has not been studied in patients with a history of pancreatitis; consider another antidiabetic therapy. Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. Not a substitute for insulin. Has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. Not for patients with pre-existing severe gastrointestinal disease. Has not been studied in combination with basal insulin.

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Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with Trulicity. Counsel regarding the risk factors and symptoms of thyroid tumors.

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

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

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

Please see Important Safety Information continued on following page.

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Important Safety Information, continued

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

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

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

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

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

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

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

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

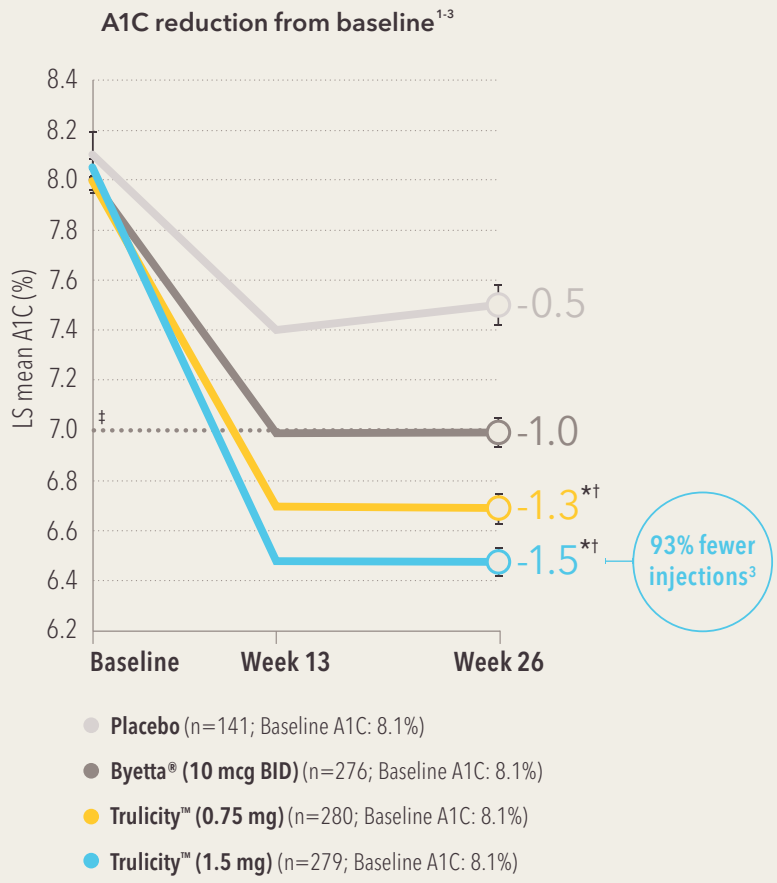
Nursing Mothers: It is not known whether Trulicity is excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue Trulicity taking into account the importance of the drug to the mother.

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

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

DG HCP ISI 12NOV2014

Once-weekly Trulicity showed significant A1C reduction[1]



Data represent least-squares mean ± standard error.

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

† Multiplicity-adjusted 1-sided *P* value <.001 for superiority of Trulicity vs placebo for A1C. Mixed model repeated measures analysis.

After 26 weeks, placebo-treated patients were switched in a blinded fashion to Trulicity 1.5 mg or Trulicity 0.75 mg.

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

- Recommended starting dose is 0.75 mg. Dose can be increased to 1.5 mg for additional A1C reduction
- 52-week, randomized, placebo-controlled phase 3 study (open-label assignment to Byetta or blinded assignment to Trulicity or placebo) of adult patients with type 2 diabetes treated with maximally tolerated metformin (≥1500 mg/day) and Actos® (up to 45 mg/day)
- Primary objective was to demonstrate superiority of Trulicity 1.5 mg vs placebo on change in A1C from baseline at 26 weeks (-1.5% vs -0.5%, respectively; difference of -1.1%; 95% CI [-1.2, -0.9]; multiplicity-adjusted 1-sided *P* value <.001; analysis of covariance using last observation carried forward); primary objective met

References

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

once weekly
trulicity™
(dulaglutide) injection
0.75 mg/0.5 mL, 1.5 mg/0.5 mL

Trulicity™

(dulaglutide)

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

WARNING: RISK OF THYROID C-CELL TUMORS

• In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies.

• Trulicity is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with Trulicity. Counsel regarding the risk factors and symptoms of thyroid tumors.

INDICATIONS AND USAGE

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

Limitations of Use:

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Risk of Thyroid C-cell Tumors: In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. Glucagon-like peptide (GLP-1) receptor agonists have induced thyroid C-cell adenomas and carcinomas in mice and rats at clinically relevant exposures. It is unknown whether Trulicity will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of this signal could not be determined from the clinical or nonclinical studies. One case of MTC was reported in a patient treated with Trulicity. This patient had pretreatment calcitonin levels approximately 8 times the upper limit of normal (ULN). Trulicity is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the risk for MTC with the use of Trulicity and inform them of symptoms of thyroid tumors (eg, a mass in the neck, dysphagia, dyspnea, persistent hoarseness). The role of serum calcitonin monitoring or thyroid ultrasound monitoring for the purpose of early detection of MTC in patients treated with Trulicity is unknown. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin as a screening test for MTC and a high background incidence of thyroid disease. Very elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. Patients with thyroid nodules noted on physical examination or neck imaging should also be referred to an endocrinologist for further evaluation. **Pancreatitis:** In Phase 2 and Phase 3 clinical studies, 12 (3.4 cases per 1000 patient years) pancreatitis-related adverse reactions were reported in patients exposed to Trulicity versus 3 in non-incretin comparators (2.7 cases per 1000 patient years). An analysis of adjudicated events revealed 5 cases of confirmed pancreatitis in patients exposed to Trulicity (1.4 cases per 1000 patient years) versus 1 case in non-incretin comparators (0.88 cases per 1000 patient years). After initiation of Trulicity, observe patients carefully for signs and symptoms of pancreatitis, including persistent severe abdominal pain. If pancreatitis is suspected, promptly discontinue Trulicity. If pancreatitis is confirmed, Trulicity should not be restarted. Trulicity has not been evaluated in patients with a prior history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. **Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin:** The risk of hypoglycemia is increased when Trulicity is used in combination with insulin secretagogues (eg, sulfonylureas) or insulin. Patients may require a lower dose of sulfonylurea or insulin to reduce the risk of hypoglycemia. **Hypersensitivity Reactions:** Systemic hypersensitivity reactions were observed in patients receiving Trulicity in clinical trials. If a hypersensitivity reaction occurs, the patient should discontinue Trulicity and promptly seek medical advice. **Renal Impairment:** In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Because these reactions may worsen renal failure, use caution when initiating or escalating doses of Trulicity in patients with renal impairment. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. **Severe Gastrointestinal Disease:** Use of Trulicity may be associated with gastrointestinal adverse reactions, sometimes severe. Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Trulicity or any other antidiabetic drug.

ADVERSE REACTIONS

Clinical Studies Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. Pool of Placebo-controlled Trials: These data reflect exposure of 1670 patients to Trulicity and a mean duration of exposure to Trulicity of 23.8 weeks. Across the treatment arms, the mean age of patients was 56 years, 1% were 75 years or older and 53% were male. The population in these studies was 69% White, 7% Black or African American, 13% Asian; 30% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8.0 years and had a mean HbA1c of 8.0%. At baseline, 2.5% of the population reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60mL/min/1.73 m^2) in 96.0% of the pooled study populations. **Adverse Reactions in Placebo-Controlled Trials Reported in ≥5% of Trulicity-Treated Patients:** Placebo (N=568), Trulicity 0.75mg (N=836), Trulicity 1.5 mg (N=834) (listed as placebo, 0.75 mg, 1.5 mg) nausea (5.3%, 12.4%, 21.1%), diarrhea[a] (6.7%, 8.9%, 12.6%), vomiting[b] (2.3%, 6.0%, 12.7%), abdominal pain[c] (4.9%, 6.5%, 9.4%), decreased appetite (1.6%, 4.9%, 8.6%), dyspepsia (2.3%, 4.1%, 5.8%), fatigue[d] (2.6%, 4.2%, 5.6%). ([a] Includes diarrhea, fecal volume increased, frequent bowel movements. [b] Includes retching, vomiting, vomiting projectile. [c] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, gastrointestinal pain. [d] Includes fatigue, asthenia, malaise.) Note: Percentages reflect the number of patients that reported at least 1 treatment-emergent occurrence of the adverse reaction. *Gastrointestinal Adverse Reactions* : In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving Trulicity than placebo (placebo 21.3%, 0.75 mg 31.6%, 1.5 mg 41.0%). More patients receiving Trulicity 0.75 mg (1.3%) and Trulicity 1.5 mg (3.5%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.2%). Investigators graded the severity of gastrointestinal adverse reactions occurring on 0.75 mg and 1.5 mg of Trulicity as "mild" in 58% and 48% of cases, respectively, "moderate" in 35% and 43% of cases, respectively, or "severe" in 7% and 11% of cases, respectively. In addition to the adverse reactions ≥5% listed above, the following adverse reactions were reported more frequently in Trulicity-treated patients than placebo (frequencies listed, respectively, as: placebo; 0.75 mg; 1.5 mg): constipation (0.7%; 3.9%; 3.7%), flatulence (1.4%; 1.4%; 3.4%), abdominal distension (0.7%; 2.9%; 2.3%), gastroesophageal reflux disease (0.5%; 1.7%; 2.0%), and eructation (0.2%; 0.6%; 1.6%). Pool of Placebo- and Active-Controlled Trials: The occurrence of adverse reactions was also evaluated in a larger pool of patients with type 2 diabetes participating in 6 placebo- and active-controlled trials evaluating the use of Trulicity as monotherapy and add-on therapy to oral medications or insulin. In this pool, a total of 3342 patients with type 2 diabetes were treated with Trulicity for a mean duration 52 weeks. The mean age of patients was 56 years, 2% were 75 years or older and 51% were male. The population in these studies was 71% White, 7% Black or African American, 11% Asian; 32% were of Hispanic or Latino ethnicity. At baseline, the population had diabetes for an average of 8.2 years and had a mean HbA1c of 7.6-8.5%. At baseline, 5.2% of the population reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR ≥60 ml/min/1.73 m^2) in 95.7% of the Trulicity population. In the pool of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed as ≥5% above. Other Adverse Reactions: *Hypoglycemia* : **Incidence (%) of Documented Symptomatic (≤70 mg/dL Glucose Threshold) and Severe Hypoglycemia in Placebo-Controlled Trials:** Add-on to Metformin at 26 weeks, Placebo (N=177), Trulicity 0.75 mg (N=302), Trulicity 1.5 mg (N=304), Documented symptomatic: Placebo: 1.1%, 0.75 mg: 2.6%, 1.5 mg: 5.6%; Severe: all 0. Add-on to Metformin + Pioglitazone at 26 weeks, Placebo (N=141), TRULICITY 0.75 mg (N=280), Trulicity 1.5 mg (N=279), Documented symptomatic: Placebo: 1.4%, 0.75 mg: 4.6%, 1.5 mg: 5.0%; Severe: all 0. Hypoglycemia was more frequent when Trulicity was used in combination with a sulfonylurea or insulin. Documented symptomatic hypoglycemia occurred in 39% and 40% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with a sulfonylurea. Severe hypoglycemia occurred in 0% and 0.7% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with a sulfonylurea. Documented symptomatic hypoglycemia occurred in 85% and 80% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with prandial insulin. Severe hypoglycemia occurred in 2.4% and 3.4% of patients when Trulicity 0.75 mg and 1.5 mg, respectively, was co-administered with prandial insulin. *Heart Rate Increase and Tachycardia Related Adverse Reactions* : Trulicity 0.75 mg and 1.5 mg resulted in a mean increase in heart rate (HR) of 2-4 beats per minute (bpm). The long-term clinical effects of the increase in HR have not been established. Adverse reactions of sinus tachycardia were reported more frequently in patients exposed to Trulicity. Sinus tachycardia was reported in 3.0%, 2.8%, and 5.6% of patient treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Persistence of sinus tachycardia (reported at more than 2 visits) was reported in 0.2%, 0.4% and 1.6% of patients treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. Episodes of sinus tachycardia, associated with a concomitant increase from baseline in heart rate of ≥15 beats per minute, were reported in 0.7%, 1.3% and 2.2% of patient treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. *Immunogenicity* : Across four Phase 2 and five Phase 3 clinical studies, 64 (1.6%) TRULICITY-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in Trulicity (ie, dulaglutide). Of the 64 dulaglutide-treated patients that developed dulaglutide ADAs, 34 patients (0.9% of the overall population) had dulaglutide-neutralizing antibodies, and 36 patients (0.9% of the overall population) developed antibodies against native GLP-1. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to dulaglutide cannot be directly compared with the incidence of antibodies of other products. *Hypersensitivity*: Systemic hypersensitivity adverse reactions sometimes severe (eg, severe urticaria, systemic rash, facial edema, lip swelling) occurred in 0.5% of patients on Trulicity in the four Phase 2 and Phase 3 studies. *Injection-site Reactions* : In the placebo-controlled studies, injection-site reactions (eg, injection-site rash, erythema) were reported in 0.5% of Trulicity-treated patients and in 0.0% of placebo-treated patients. *PR Interval Prolongation and Adverse Reactions of First Degree Atrioventricular (AV) Block* : A mean increase from baseline in PR interval of 2-3 milliseconds was observed in Trulicity-treated patients in contrast to a mean decrease of 0.9 millisecond in placebo-treated patients. The adverse reaction of first degree AV block occurred more frequently in patients treated with Trulicity than placebo (0.9%, 1.7% and 2.3% for placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively). On electrocardiograms, a PR interval increase to at least 220 milliseconds was observed in 0.7%, 2.5% and 3.2% of patients treated with placebo, Trulicity 0.75 mg and Trulicity 1.5 mg, respectively. *Amylase and Lipase Increase*: Patients exposed to Trulicity had mean increases from baseline in lipase and/or pancreatic amylase of 14% to 20%, while placebo-treated patients had mean increases of up to 3%.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Pregnancy - Pregnancy Category C: There are no adequate and well-controlled studies of Trulicity in pregnant women. The risk of birth defects, loss, or other adverse outcomes is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes to maintain good metabolic control before conception and throughout pregnancy. Trulicity should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In rats and rabbits, dulaglutide administered during the major period of organogenesis produced fetal growth reductions and/or skeletal anomalies and ossification deficits in association with decreased maternal weight and food consumption attributed to the pharmacology of dulaglutide. **Nursing Mothers:** It is not known whether Trulicity is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for clinical adverse reactions from Trulicity in nursing infants, a decision should be made whether to discontinue nursing or to discontinue Trulicity, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness of Trulicity have not been established in pediatric patients. Trulicity is not recommended for use in pediatric patients younger than 18 years. **Geriatric Use:** In the pool of placebo- and active-controlled trials, 620 (18.6%) Trulicity-treated patients were 65 years of age and over and 65 Trulicity-treated patients (1.9%) were 75 years of age and over. No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** There is limited clinical experience in patients with mild, moderate, or severe hepatic impairment. Therefore, Trulicity should be used with caution in these patient populations. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no clinically relevant change in dulaglutide pharmacokinetics (PK) was observed. **Renal Impairment:** In the four Phase 2 and five Phase 3 randomized clinical studies, at baseline, 50 (1.2%) Trulicity-treated patients had mild renal impairment (eGFR ≥60 but <90 mL/min/1.73 m^2), 171 (4.3%) Trulicity-treated patients had moderate renal impairment (eGFR ≥30 but <60 mL/min/1.73 m^2) and no Trulicity-treated patients had severe renal impairment (eGFR <30 mL/min/1.73 m^2). No overall differences in safety or effectiveness were observed relative to patients with normal renal function, though conclusions are limited due to small numbers. In a clinical pharmacology study in subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in dulaglutide PK was observed. There is limited clinical experience in patients with severe renal impairment or ESRD. Trulicity should be used with caution, and if these patients experience adverse gastrointestinal side effects, renal function should be closely monitored. **Gastroparesis:** Dulaglutide slows gastric emptying. Trulicity has not been studied in patients with pre-existing gastroparesis.

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION See FDA-approved Medication Guide

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

Eli Lilly and Company, Indianapolis, IN 46285, USA

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Additional information can be found at www.trulicity.com

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At Joslin, We're Ready to Welcome the ADA to Boston

Robert A. Gabbay, MD, PhD

ABOUT THE EDITOR

Joslin Diabetes Center

ROBERT A. GABBAY, MD, PhD

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

Our mission at Joslin Diabetes Center calls for sharing what we learn about treating diabetes, and typically our faculty does that by traveling to meetings across the country and all around the world. This year, however, we look forward to the diabetes community coming to our doorstep, when Boston hosts the American Diabetes Association's (ADA's) 75th Scientific Sessions June 5-9, 2015.

This opportunity will allow faculty and fellows from Joslin to take part in more than 50 presentations, including 31 posters and 14 oral presentations. We are very excited to announce that the ADA is presenting awards to 3 of our faculty members. One of the recipients is Lori Laffel, MD, MPH, chief of the Section on Pediatric, Adolescent and Young Adult Diabetes at Joslin, who will receive the 2015 Outstanding Physician Clinician Award. This is one of the ADA's highest awards, presented annually to an individual who is actively involved in the clinical care of patients with diabetes. Dr Laffel is the third Joslin recipient to receive this award. One of the other recipients is George L. King, MD, chief scientific officer at Joslin, who will receive the 2015 Edwin Bierman Award for his exceptional achievements in the field of diabetes-related macrovascular complications and related risk factors.

Two of our faculty will chair panels: Gordon C. Weir, MD, head of Section on Islet Cell and Regenerative Biology at Joslin, will lead a discussion titled "Transplantation at the Bench." And Laurie Goodyear, PhD, head of the section on Integrative Physiology and Metabolism at Joslin, will chair the panel, "Effects of Exercise on Non-Muscle Targets."

I am excited about the diversity of our oral presentations this year. A look at the schedule reveals the breadth of Joslin's work in the basic science of diabetes, from our increased understanding of the role of genetics, to insulin regulation, to the origins of diabetes at its earliest stages. We are also doing critical work in discovering how diabetes affects long-term health, and we are learning how we, as physicians, can engage our patients to change their behaviors by giving them the opportunity to lead longer, healthier lives.

My presentations at the ADA will be of interest to those who are following the national movement away from fee-for-service and toward a fee-for-value model, with a particular focus on patient-centered diabetes care. I will be leading the Clinical Endocrinology, Health Care Delivery and Public Health Interest Group in an engaging discussion around "Innovative Diabetes Care Delivery Models." In addition, I will be taking part in a symposium titled "Population Management—Coordinating High-Value Diabetes Care in Diverse Settings," in which I will speak on state-based initiatives. These sessions should be of great interest to you and your colleagues.

Other highlights include Dr Goodyear's presentation, "Browning of Fat and Insulin Action." This is an area that holds promise in the development of new targets for weight management. Osama Hamdy, MD, PhD, medical director of our Obesity Clinical Program at Joslin, will present on his abstract titled "The Long-term Effects of Intensive Lifestyle Intervention on Cardiovascular Risk Factors in Patients with Diabetes in a Real-World Clinical Practice: a 5-Year Longitudinal Study." This abstract was selected to receive the Michaela Modan Memorial Award and was chosen from the top abstracts submitted to the ADA in the areas of human studies on the epidemiology, complications, and prevention of diabetes.

Our researchers continue to focus on identifying a diabetes cure, and 2 faculty from the Section on Islet Cell and Regenerative Biology will give talks on promising approaches to beta cell therapy that utilize Joslin's unique reset, regulate, and regenerate approach. These researchers include Mary R. Loeken, PhD, investigator in the section on Islet Cell Biology and Regenerative Medicine at Joslin, Ercument Dirice, PhD, research fellow in the section on Islet Cell and Regenerative Biology at Joslin, and others.

Representing Joslin from the Section on Vascular Cell Biology are investigator Jennifer K. Sun, MD, MPH, who will discuss "Strengthening Our Defense Against Diabetic Retinopathy," and Qian Li, MD, PhD, postdoctoral fellow at Joslin, who will share the result of, "Differential Outcomes of Restenosis and Atherosclerosis in Mice with Deletion of Insulin Receptors in Vascular Smooth Muscle Cells."

From Genetics and Epidemiology, Jan Skupien, MD, research fellow at Joslin, will give a talk based on long-term kidney studies at Joslin: "Interaction between Genetic Variants and Glycemic Control in the Pathogenesis of Renal Decline in Type 1 Diabetes Patients from the Joslin Proteinuria Cohort." Stephan Kissler, PhD, assistant investigator in the section of Immunobiology at Joslin, will offer insights in his lecture "High-Throughput Functional Validation of Genetic Findings."

Medha N. Munshi, MD, director of the Geriatrics Program at Joslin, will discuss how diabetes affects some of our seniors in her presentation, "Is Life Significantly Worse for Patients with Comorbid Diabetes and Dementia?"

Of course, the best way to hear these wonderful talks is to come to Boston. If you haven't registered, there's still time. Online registration closes May 28, 2015. To learn more, visit http://professional.diabetes.org/Congress_Display.aspx?TYP=9&CID=95010. We hope to see you there! **EBDM**

POLICY

ADA, AMA, and YMCA Praise Introduction of Medicare Diabetes Prevention Act

Mary K. Caffrey

A trio of well-known groups with different healthcare missions praised the recent introduction of federal legislation to prevent type 2 diabetes mellitus (T2DM) among the nation's seniors, with an estimate putting the bill's potential savings at $1.3 billion over 10 years.

On April 30, 2015, the American Diabetes Association, the American Medical Association (AMA), and the YMCA of the USA called attention to the latest effort to pass the Medicare Diabetes Prevention Act, which would require coverage of the Diabetes Prevention Program for beneficiaries at high risk of developing T2DM.[1]

The legislation has been introduced in the US House of Representatives as H.R. 2101 and in Senate as S. 1131. Sponsors are Representatives Susan Davis, D-California and Peter King, R-New York, and Senators Al Franken, D-Minnesota, and Susan Collins, R-Maine, respectively. The act was also introduced in the last session of Congress.

Support for fighting diabetes has significant bipartisan support in Congress, even though bills have not made it past the finish line. Collins was also a prime sponsor of legislation introduced late in the last session to require Medicare to pay for continuous glucose monitoring technology. That legislation also had a number of cosponsors from both parties in both the House and Senate.

The current legislation comes shortly after the CDC and AMA launched Prevent Diabetes STAT, a high-profile effort to identify persons with prediabetes and intervene before they progress to full-blown diabetes (**see cover story**). CDC's partnership with YMCA on the Diabetes Prevention Program (DPP) has shown that interventions in individuals with prediabetes can reduce their risk for T2DM by 58% with lifestyle changes including improved nutrition, increased physical activity, and weight loss of 5-7%. CDC and AMA are also working to get commercial payers to cover the DPP.

Results were even stronger for seniors. Participants over the age of 60 years reduced their risk for T2DM by 71%. Research has shown that in a community setting, these results can be replicated in a group setting for a relatively modest cost of $300 to $400 per person—far less than the long-term costs of complications from diabetes. The 10-year savings estimate was calculated by Avalere Health. **EBDM**

REFERENCE

The American Diabetes Association, American Medical Association and the YMCA of the USA applaud the introduction of the Medicare Diabetes Prevention Act [press release]. http://www.ama-assn.org/ama/pub/news/news/2015/2015-04-30-ama-ada-ymca-medicare-diabetes-prevention-act.page. Chicago, IL: AMA Newsroom; April 30, 2015.

States With Medicaid Expansion Find 23% Rise in T2DM Diagnoses Among Enrollees, While Rest See No Increase

Mary K. Caffrey

The findings in Diabetes Care *served as early confirmation of what some had feared: a bifurcated Medicaid system will lead to an America of haves and have-nots in healthcare.*

VIVIAN FONSECA, MD

Vivian Fonseca, MD, professor of Medicine and Pharmacology at Tulane University School of Medicine, is a coauthor of the study that appeared in *Diabetes Care*. Higher levels of diabetes diagnoses in states with Medicaid expansion may have exceeded expectations, he told *EBDM.*

While many studies were released in conjunction with the 5-year anniversary of the Affordable Care Act (ACA), the results published March 22, 2015, in *Diabetes Care* hit like a thunderclap. An analysis of data from a national laboratory testing company showed a 23% rise in type 2 diabetes mellitus (T2DM) diagnoses among Medicaid enrollees in states that expanded the program in the law's first year. In states that did not expand Medicaid, the number of new diagnoses among enrollees barely budged (up 0.4%).[1]

This divide appeared even though the states that did not expand Medicaid include many with high existing rates of T2DM; many are in the Deep South, across a region recognized by CDC as the "diabetes belt." (See **FIGURES 1** and **2**.) There was really only 1 conclusion, the authors wrote. "I cannot think of any other explanation except these people have now got health insurance," said coauthor Vivian Fonseca, MD, professor of medicine at Tulane University.[2]

RESULTS OF THE STUDY

When the ACA passed in 2010, its supporters sought to expand Medicaid to all households with incomes up to 138% of the federal poverty line. But the US Supreme Court ruled otherwise in 2012; because the healthcare program for the poor is jointly funded by states and the federal government, the justices chose to let states decide on their own whether to extend benefits to the next income tier.

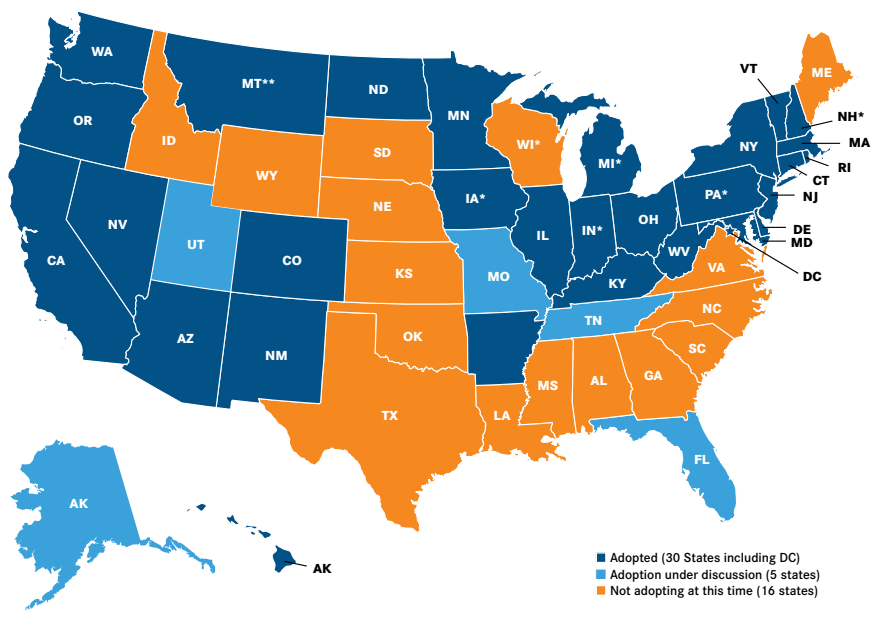
By January 2014, when the first ACA policies took effect, 26 states and the District of Columbia had expanded Medicaid, while 24 had not. This allowed researchers to directly compare the effect of expansion on the number of new T2DM diagnoses that would appear among Medicaid enrollees aged 19 to 64 years, by using laboratory records from Quest Diagnostics.[1]

In an interview with *Evidence-Based Diabetes Management*, Fonseca said the study itself was straightforward: "What is the impact going to be on diabetes as more and more people get insurance?" For all the debate about the ACA, Fonseca said he was strictly interested in the changes in patterns surrounding the disease. "My interest is scientific. It has nothing to do with politics," he said.

Researchers stripped away identification information from lab results. Then they identified new cases of diabetes by the presence of either an *International Classification of Diseases, Ninth Revision* diagnosis code for the disease or a glycated hemoglobin test result of >6.4%. These results would have to have occurred within the first 6 months of 2014, and been absent during the preceding year, to count as a new T2DM diagnosis. Through this method, researchers identified 215,398 patients who were newly diagnosed with T2DM during 2013—the control period—and 218,890 who met the definition in 2014, the study period. Overall, this was a 1.6% increase.[1]

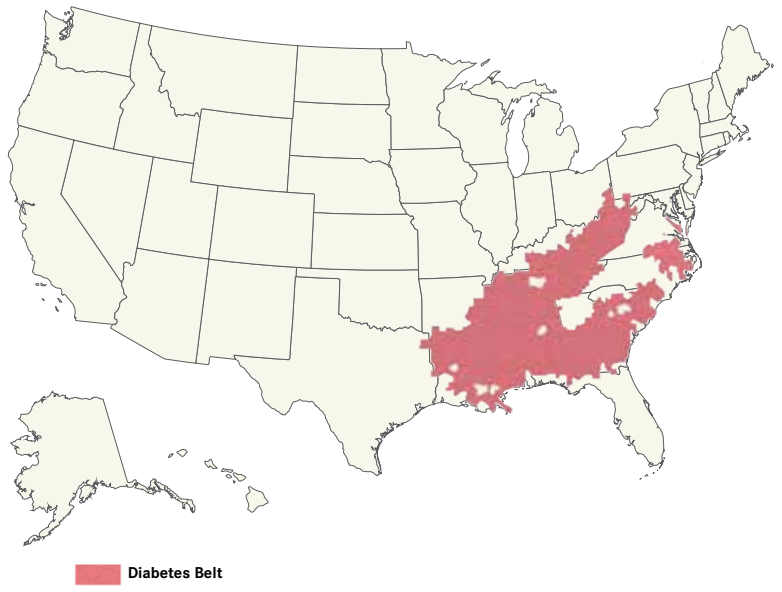
Then, researchers identified 26,237 Medicaid patients with new T2DM diagnoses in 2013, compared with 29,673 in 2014, for an increase of 13% in the Medicaid population. The number of Medicaid patients with new diagnoses increased by 23% in the 26 states plus the District of Columbia that expanded Medicaid. In these states, the difference was 14,625 diagnoses in 2013, compared with 18,020 diagnoses in 2014. In the other 24 states, the difference was 11,612 in 2013 vs 11,653 patients in 2014, for a rate of 0.4%.[1] "In some ways, the differences are probably higher than what we anticipated," Fonseca told *EBDM*.

FIGURE 1. Status of Medicaid Expansion



SOURCE: Kaiser Family Foundation.

FIGURE 2. America's Diabetes Belt



SOURCE: CDC.

FROM THEORY TO REALITY

The *Diabetes Care* results add weight to concerns that some experts expressed last year in interviews with *EBDM*: the ability of the working poor to access treatment for diabetes will vary depending on where they live, due to state-level decisions on Medicaid expansion.

Krista Maier, associate director of public policy for the American Diabetes Association (ADA), told *EBDM* in May 2014 that states that did not extend Medicaid to those in the next tier above 100% of the poverty line were effectively locking this group out of health coverage. Because the ACA assumed all states would expand Medicaid, there was no provision for financial assistance for consumers if their states opted against expansion, she explained.[3] According

to the Kaiser Family Foundation, an estimated 3.7 million adults were in this "coverage gap" as of March 2015.[4]

The irony, Maier noted in 2014, is that states that refuse to expand Medicaid are required to support those with diabetes who become disabled due to amputations, blindness, or other complications. "When you can't afford the care to manage your disease, you scale back the care. Without adequate care, you increase risk of complications," she said. "The states that don't expand Medicaid are, essentially, waiting for the person to become so sick they are disabled to be eligible. If they expanded eligibility these people could receive care before they are disabled."[3]

Maier's observations are noteworthy in light of the *Diabetes Care* findings that 35.4% of the new T2DM diagnoses in expansion states were among those aged 19 to 49 years. If persons with T2DM in this age group can achieve better glycemic control and avoid long-term complications, there would be opportunities for medical savings and avoidance of lost productivity. In 2013, the ADA determined that these 2 items cost the United States $245 billion a year.[5]

Before results like those published in *Diabetes Care*, however, any discussion about whether failure to expand Medicaid could be linked to health outcomes was strictly theoretical. Now, that is no longer the case. Larry Levitt, senior vice president of the Kaiser Family Foundation, told *The Washington Post* that "People can really start to assess what the law means in tangible terms, like how many people have gotten insurance, and what that coverage means for their finances and their health."[2]

"MISSED OPPORTUNITY"

Robert Ratner, MD, chief medical officer for the ADA, was among those who pointed out the irony of the findings: the states that have not expanded Medicaid are those that have the largest populations with the disease, and thus may have the largest numbers of people living with T2DM who don't know it. Catching the disease early creates the opportunity to reduce long-term medical costs, he said.[6]

When the results were released, Ratner told National Public Radio, "Those states that did not expand Medicaid missed that opportunity and they still have large percentages of people, perhaps as large as 20%, living with the disease."[6]

An accompanying editorial in *Diabetes Care*, coauthored by the journal's editor in chief, William T. Cefalu, MD, called on policy leaders to set aside politics and make healthcare decisions based on facts. "The data demonstrate the benefits of Medicaid expansion, yet nearly half of our states have chosen not to expand this benefit to their citizens. The real-world benefits and costs of Medicaid expansion merit additional research and civil debate. And perhaps most important, their results should be used to guide health policy to address the growing burden of chronic diseases."[7] **EBDM**

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USPSTF Evidence Review Could Lead to Revised Screening Guidelines

Mary K. Caffrey

A look at the most recent evidence on how to identify those at risk for diabetes could lead the US Preventive Services Task Force (USPSTF) to alter the way the healthcare system screens for prediabetes.[1] In October 2014, a draft guideline shifted the focus from persons with elevated blood pressure (BP) to those with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).[2]

A USPSTF literature review, published April 14, 2015, in the *Annals for Internal Medicine*,[1] found that millions of Americans could avoid the progression to diabetes if screening for abnormal glucose became the routine for adults 45 years and older (screening would be recommended for younger adults with risk factors).[3]

The review did not find a 10-year mortality benefit from screening. However, screening for IFG or IGT did help delay disease progression, which could have important implications for managed care. The total cost associated with diabetes in the United States, estimated at $245 billion in 2012,[4] includes the cost of treating the disease and its complications, such as kidney failure and blindness, as well as costs arising from lost productivity, including disability costs incurred by patients unable to work.

Early identification of persons with prediabetes, along with education and intervention, has received priority treatment from both the medical and public health communities, through the launch of Prevent Diabetes STAT by the American Medical Association and CDC.[5]

The literature review synthesized 16 trials that consistently found the treatment of IFG or IGT to be associated with a delayed progression to diabetes. Most trials of treatment for either condition found no effects on all-cause or cardiovascular mortality.

In 2008, the USPSTF issued a B recommendation for diabetes screening in asymptomatic adults with sustained BP greater than 135/80 mm Hg. The recommendation was based on the ability of screening to identify those with diabetes, as well as evidence that treating BP was associated with reduced risk for cardiovascular events. At that time, the USPSTF did not find sufficient evidence to include screening for adults without elevated BP.[1] **EBDM**

TABLE. Test Values for Normal Glucose Metabolism, IFG or IGT, and T2DM[a]

Test	Normal	IFG or IGT	T2DM
Glycated hemoglobin	<5.7%	5.7% to 6.4%	>6.5% (on 2 separate tests)
Random plasma glucose	<140 mg/dL	140 to 199 mg/dL	>200 mg/dL (suggestive)
Fasting plasma glucose	<100 mg/dL	100 to 125 mg/dL	>126 mg/dL
2-hour OTT	<140 mg/dL	140 to 199 mg/dL	>200 mg/dL

Source: American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2012;35(suppl 1) :S64-71. [a]FG indicates impaired fasting glucose; IGT, impaired glucose tolerance; OTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus.

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Preventing Ketoacidosis Complications in Diabetes

Surabhi Dangi-Garimella, PhD

Diabetic ketoacidosis (DKA)—a hyperglycemic crisis most commonly associated with type 1 diabetes mellitus (T1DM)—is often the first symptom of diabetes to appear in the undiagnosed population. Managing the condition effectively to prevent incidence is important because of the associated morbidity and resulting economic impact.[1] Studies have shown that hospitalizations resulting from DKA amount to an annual cost of more than $2.4 billion in the United States.[1]

THE PATHOLOGY BEHIND KETOACIDOSIS?

Reduced concentrations of effective insulin and increased amounts of counter-regulatory hormones. Since the body cannot break down and use sugar as an energy source, it draws energy from fat tissue; increased lipolysis releases free fatty acids in the blood and causes oxidation of hepatic fatty acids to ketone bodies, resulting in ketonemia and metabolic acidosis.[1,2]

DKA is also observed in type 2 diabetes mellitus (T2DM) patients, most often a result of uncontrolled blood sugar, missed doses of insulin, or a comorbidity. If left untreated, DKA can lead to cerebral edema, heart attack, pulmonary or gastrointestinal complications, or kidney failure.[2,3]

Most risk factors associated with diabetic ketoacidosis in young children cannot be altered. However, identifying those most vulnerable might help direct services to those most likely to have an incident.

INCIDENCE OF DKA

Multiple studies have determined that socioeconomic status can greatly influence patients' insulin compliance. One investigation, which focused on adult patients from an inner-city area, found poor compliance to be dictated by behavioral, socioeconomic, psychosocial, and educational factors. The authors concluded that culturally appropriate interventions and education programs could remedy DKA recurrence in this population.[4]

DKA is quite common in the younger population, according to a study published last year in *Pediatrics* that reported results from a multi-center surveillance conducted between 2002 and 2010 across the United States. The analysis, based on data from 5615 individuals under 20 years of age, revealed an increased incidence of DKA in the T1DM population compared with T2DM, indicating a possible earlier diagnosis or improved detection of the T2DM. The survey found that diagnosis of DKA among youth with T1DM in the Unites States remained high compared with other developed countries, with the highest incidence observed in:

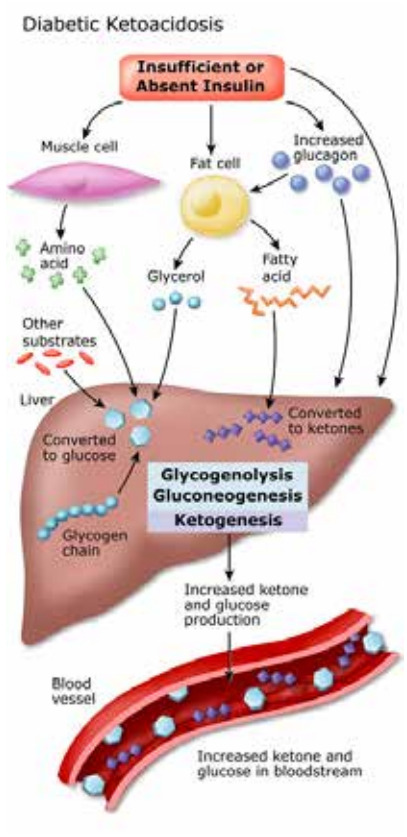
- Children less than 5 years of age
- Non-white ethnic groups
- Youth not covered by private health plans
- Youth from low-income families.

Based on their findings, the authors recommended improving people's awareness of the ways to recognize the signs and symptoms of diabetes, along with improving the population's access to healthcare. Referring to the provisions of the Affordable Care Act (ACA) that would make healthcare more accessible, the authors predicted a reduction in DKA rates, but warned that minority groups might need additional outreach activities to achieve significant improvements.[5]

A more recent report in JAMA, based on data collected between 1998 and 2012 in Colorado, showed that DKA was present in nearly 40% of those newly diagnosed with T1DM before age 18 years, and the incidence increased from 29.9% in 1998 to 46.2% in 2012. Significant risk factors included younger age and race (African American). Conversely, those covered by private insurance had a lower risk of DKA, as were youth who had a first-degree relative diagnosed with T1DM.[6]

However, between 2007 and 2012, private insurance was associated with a 2.5% increase in DKA per year, and public insurance a 1.3% *decrease* per year. The authors wrote: "The recent increase of DKA incidence among youth with private insurance may be related to proliferation of high-deductible health plans." While the authors acknowledged that it may not be possible to generalize results gathered from a single state, they suggested that additional studies are needed to make clear both the reasons behind the increase in DKA incidence and the interventions necessary for reducing incidence.[6]

FIGURE. Pathology of Diabetic Ketoacidosis



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The results might actually be more generalizable than the authors presumed. A retrospective evaluation of 167 patients admitted to a pediatric intensive care unit in Charleston, West Virginia, identified socioeconomic factors as major contributors to children (average age, 13.5 years) being admitted for DKA. High glycated hemoglobin, race (African American), and insurance coverage through Medicaid/CHIPS (indicative of low socioeconomic status) were high risk factors for children being diagnosed with DKA.[7]

PREVENTING DKA

A look at some of the risk factors associated with the incidence of DKA among young children indicates that most of these variables cannot be controlled. Race and socioeconomic strata, for example, cannot be altered. However, identifying the population most vulnerable to a particular condition might help direct services to a specific subset of the population and help reduce incidence. In this case, raising awareness about DKA, educating patients on diabetes self-management, and ensuring appropriate interventions could prevent incidence of this condition in the young T1DM population. Equally important is ensuring adequate access to healthcare so that patients don't miss or skip medication doses.

Importantly, provisions within the ACA have included DKA—a manifestation of poor glycemic control—in the list of hospital-acquired conditions (HACs). HACs are program measures that rate a hospital's performance and determine their inpatient reimbursement to ensure that providers pay attention to preventable conditions.[8] **EBDM**

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THE AMERICAN JOURNAL OF MANAGED CARE

More Young Adults Would Take Statins Under Pediatric Guidelines, Study Finds

Mary K. Caffrey

When treating a person aged 17 to 21 years, which clinical guidelines should apply? Should physicians follow pediatric guidelines, or those for adults? Would it make a difference?

In the case of statins, 400,000 more young people in this age group might be taking them for elevated levels of low-density lipoprotein (LDL) cholesterol if physicians followed pediatric guidelines, according to a study published April 6, 2015, in *JAMA Pediatrics*.

Researchers led by Holly C. Gooding, MD, MSc, performed a cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) population from 1999-2012, capturing 6338 participants in the United States aged 17 to 21 years. Using an algorithm from the National Heart, Lung, and Blood Institute and applying the 2013 guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA), the researchers extrapolated their results across the 20.4 million young adults in the age group.

The authors noted that cardiovascular risk can emerge in late adolescence, just as young people leave behind their pediatrician and find a new primary care doctor. The authors also discussed the uproar that followed the release of the 2013 ACC/AHA guidelines, which some felt would over-treat cardiovascular disease, as well as the confusion of reconciling the pediatric and adult guidelines.

Until this study, they wrote, no one had reported on the discrepancies between pediatric and adult guidelines that must be considered when treating adolescents transitioning to young adulthood.

Of the study group participants, 2.5% would qualify for statin treatment under the pediatric guidelines, compared with only 0.4% under the adult guidelines. Those who met the pediatric guidelines had a lower mean LDL cholesterol level (167.3 vs 210.0 mg/dL), but a higher proportion of their group had other cardiovascular risk factors such as smoking, hypertension, and obesity, than those who met the adult guidelines. This translates into 483,500 of the population in the 17-to-21-year age group who would take statins under pediatric guidelines, compared with 78,200 under the adult guidelines.

"Given the current uncertain state of knowledge and conflicting guidelines for treatment of lipid levels among youth aged 17 to 21 years, physicians and patients should engage in shared decision making around the potential benefits, harms, and patient preferences for treatment," the researchers concluded.

"The 2013 American College of Cardiology and American Heart Association guidelines recommend shared decision making with patients for whom data are inadequate, including young people with a high lifetime risk for atherosclerotic cardiovascular disease. Patients and clinicians should clearly address other modifiable risk factors, including optimizing diet, exercise, and weight, and promoting abstinence from tobacco, as strongly recommended by both the pediatric and adult guidelines." **EBDM**

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JAMA Study Reports Potential for Using Insulin to Prevent T1DM in High-Risk Children

Mary K. Caffrey

High doses of oral insulin given to children with a genetic risk of developing type 1 diabetes mellitus (T1DM) produced immune responses that suggest this therapy could be a way to prevent the disease.

Results of the pilot study were reported in the April 21, 2015, issue of *JAMA*, along with an editorial calling for a phase 3 trial based on the findings. The editorial said future studies should include children even younger than the small group of 2-to-7-year-olds who participated in the pilot, called Prevention Trial-Type 1 (Pre-POINT).[1,2]

T1DM can be detected before children develop symptoms, by the presence of islet autoantibodies. The thinking behind preventive therapy, therefore, is that triggering an immune response with insulin before antibodies appear can create a protective effect, keeping T1DM at bay. A child whose parents or older siblings have the disease would be among those considered at high genetic risk for T1DM and thus a target for preventive therapy.

Ezio Bonifacio, PhD, of the DFG Center for Regenerative Therapies Dresden, Technische Universitat Dresden, Germany, and colleagues randomly assigned genetically at-risk children who were autoantibody negative to receive oral insulin at varying doses or to receive a placebo, once a day for 3 to 18 months. Fifteen children receive an insulin dose and 10 received the placebo. The study took place between 2009 and 2013 in Germany, Austria, and the United States.[1]

Immune responses were as follows:

- In placebo-treated children, 2 of 10 (20%)
- In those treated with 2.5 mg insulin, 1 of 6 (16.7%)
- In those treated with 7.5 mg, 1 of 6 (16.7%)
- In those treated with 22.5 mg, 2 of 6 (33.3%)
- In those treated with 67.5 mg, 5 of 6 (83.3 %).[1]

There was no difference in the number of adverse events between the insulin or placebo groups, and no hypoglycemia occurred.

"The Pre-POINT pilot study demonstrated that daily oral administration of 67.5 mg of insulin to genetically at-risk healthy children without signs of islet autoimmunity resulted in an immune response without hypoglycemia. The immune response observed in insulin-treated children did not display the features typically associated with type 1 diabetes," the authors wrote.

In the accompanying editorial, Jay S. Skyler, MD, noted that the pilot study involved children at the greatest genetic risk, and a more definitive study would need to capture those at risk levels not quite as high. He also discussed whether children under age 2 years could take part, since "Peak incidence of islet autoantibodies occurs between 6 months and 2 years."[2]

Despite hurdles such as how to administer an oral insulin, researchers would want to include children before seroconversion, and thus would need to include children younger than 12 months. It's now possible, Skyler wrote, to identify those children who are at risk of developing T1DM.

"What's missing are interventions to arrest this process prior to irreversible damage to the pancreatic beta cell," and the Pre-POINT trial created evidence for a clinical trial to develop such an intervention, Skyler wrote.[2] **EBDM**

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Toujeo and Afrezza: New and Improved Insulins, Limited by FDA Labeling Constraints

Andrew Smith

RACHELE BERRIA, MD, PHD

"Healthcare providers don't seem to anticipate that patients will see much of a need to move away from injections, but actual patients see this as a valuable feature."

Existing treatments are effective enough to control diabetes in most patients, but drug makers spend huge sums to keep developing new products and improving old ones.

Indeed, Sanofi just rolled out 2 novel versions of the very oldest diabetes treatment, an insulin glargine formulation called Toujeo and an inhalable form of human insulin called Afrezza.

Sanofi officials say both products will benefit large numbers of insulin users with both type 1 and type 2 diabetes mellitus (T1DM, T2DM). Outsiders express a wide range of opinions.

Trial data indicate that Toujeo controls glycated hemoglobin (A1C) levels about as well as Lantus, an insulin glargine formulation approved in the year 2000 that has just lost patent protection after years of blockbuster sales. Toujeo lasts longer than Lantus, however.[1] It also provides the body a steadier stream of insulin[1] and is associated with a significantly lower risk of nocturnal hypoglycemia.[1]

Afrezza performed similarly in a phase 3 trial. It roughly matched an existing competitor, insulin aspart (Novolog), in A1C reduction, and slightly outperformed it in several secondary ways. Afrezza use was associated with less hypoglycemia, lower fasting blood glucose, and slight weight loss rather than slight weight gain. It also reached peak levels very quickly, in just 12 to 14 minutes on average.[2]

That said, Afrezza's medical importance will likely hinge on something that no trial can measure: how the change from injection to inhalation affects patient behavior. If the delivery method inspires patients to medicate themselves more consistently, Afrezza could produce huge health benefits. If patients use Afrezza like they use insulin aspart (a fast-acting insulin analogue), the new product could prove to be an expensive convenience.

Financial analysts mostly predict solid but unspectacular sales for both drugs, in part because federal regulations forbid Sanofi from touting the comparative advantages of either drug. (The FDA did not allow language about less hypoglycemia in the label it approved, and therefore Sanofi cannot mention it in language it uses to promote the drug.)

Consensus estimates reported by Bloomberg predict annual Toujeo sales will reach about $1.3 billion by 2020[3]—far below the $7.1 billion that Lantus generated in 2014. As for Afrezza, annual projections range from a paltry $182 million up to $2 billion, with the median in the $600-million range. The treatment's unexpectedly poor performance during its first month on the market led Goldman Sachs to cut its annual sales projections by $1 billion.[4]

In other respects, however, both medications have gotten a good reception.

"The response to Afrezza on social media has been tremendous," Rachele Berria, MD, PhD, who heads the Diabetes Medical Unit for Sanofi US, told *Evidence-Based Diabetes Management* in an interview. "Healthcare providers don't seem to anticipate that patients will see much of a need to move away from injections, but actual patients see this as a valuable feature."

Berria says the company will study real-life Afrezza use to see if patient enthusiasm translates into patient compliance, and that it will follow real-world Toujeo users to measure the practical effect of its longer, steadier flow of medication. "The goal in treating diabetes is to avoid peaks and valleys in both insulin and sugar, and Toujeo does that to a degree that once seemed impossible," she said. "There's no insulin spike when each new injection gets absorbed, and there's no loss of efficacy in the final few hours. It's a big stride forward from Lantus."

Physicians have been using insulin to treat diabetes since 1922, when Frederick Banting and Charles Best injected the hormone into a diabetic teenager at a hospital in Toronto. Eli Lilly began producing it commercially within the year, and diabetes was transformed, virtually overnight, from a speedy death sentence to a chronic condition.[5]

Intermediate-acting Neutral Protamine Hagedorn (NPH) insulin arrived about a quarter-century later, in 1950. Long-acting insulin, on the other hand, didn't reach patients until 2000, when Lantus went on sale in the United States and Europe.

The new drug reduced A1C levels about as much as NPH insulin, but trials demonstrated that it produced a greater reduction in fasting plasma glucose and fasting blood glucose as well as a far lower risk of nocturnal hypoglycemia.[6]

The other big advantage of Lantus was the convenience of longer action. Patients who had spent years toting around basal insulin and setting alarms for midday injections suddenly had nothing to carry and nothing to remember except a single injection before bed. By then, of course, insulin was not the only effective treatment for T2DM. The FDA had approved metformin in 1994, and its huge success spurred drug companies to develop the other oral treatments that now crowd the market.

Many of these treatments are quite effective, especially when used in combination. Indeed, if used properly, their excellent disease control could greatly reduce diabetic complications and the need for new drugs.

Yet pharmaceutical companies continue developing treatments like Toujeo and Afrezza because a huge percentage of diabetics fail to control their condition with current options. A recent study that examined records from more than 43,000 patients found that less than 55% of all Americans who have been diagnosed with diabetes, and prescribed medication to control blood sugar, actually manage to keep their A1C level under 7%.[7]

The main cause of this problem seems to be patient behavior. Studies have found that patient adherence to oral treatment protocols can range from more than 90% down to just over 50%. Strict adherence to guidelines concerning injectable medications and proper diet tends to be lower, while strict adherence to guidelines concerning moderate, regular exercise and blood sugar checks is downright rare.[8] The chance that any patient will adhere perfectly to a complex regimen is low, and studies of people with all types of chronic disease have typically found that only about half of them will make a serious effort to manage their condition.[8]

The consequences of this behavior are dire.

Diabetes is the nation's seventh-leading cause of death. It increases the risk of stroke (by 50%), heart attack (by 80%), and death from cardiovascular disease (by 70%). It is also the leading cause of kidney failure and non-traumatic lower limb amputation. The American Diabetes Association estimates that the direct medical cost of treating diabetes reached $176 billion in 2012, and indirect costs such as lost productivity added another $69 billion to the tally.[9]

Studies have demonstrated that increased adherence to a treatment regimen can reduce A1C levels,[10] and many other studies have shown that A1C reductions prevent complications. A 1% reduction in A1C is associated with a 14% reduction in the risk of heart attack and a 40% reduction in the risk of eye, kidney, and nerve disease.[11] (Logic says that better adherence would also slash healthcare costs, but the findings from research on that topic are mixed.[10])

A number of experiments have tested different strategies for improving adherence to existing treatment regimens. Many have failed, but many others have produced significant gains, at least over the study period, with simple approaches such as asking pharmacists to provide patients a little extra information.[12] While some researchers continue to study ideas for motivating patients, others work to improve treatments.

Some people, for example, respond poorly to existing medications, so even if patients used existing options perfectly, there would still be a need for more effective options. The biggest need, however, appears to be medications that promote compliance by making treatment regimens less arduous and more tolerable. Only real-world use will show if Toujeo and Afrezza meet that second need, but there are several reasons for hope.

For one, the reduction in nocturnal hypoglycemia associated with using Toujeo rather than Lantus is reasonably large. A meta-analysis of 3 of the drug's phase 3 trials found a 31% reduction in such reactions among 2476 patients (risk ratio, 0.69; 95% CI, 0.57-0.84; $P = .0002$).[13]

While the biggest original selling point for Lantus may have been the relatively low rate of nocturnal hypoglycemia, low blood sugar remains a serious problem. Hypoglycemia is the primary cause of roughly 282,000 emergency department visits each year,[9] and many patients fear it enough to risk high blood sugar by taking less insulin than their doctors prescribe.[14]

Thus, the lower nocturnal hypoglycemia incidence associated with Toujeo could produce 2 distinct benefits for patients who switch from Lantus:

- a reduction in hypoglycemia among those who always used a full dose, and
- a reduction in hyperglycemia

among those who only begin taking a full dose after the switch. (Sanofi's inability to advertise the lower hypoglycemia risk in the United States may curtail its potential for improving compliance here, but Toujeo's relative safety may improve patient behavior in Europe, where the approved label mentions the reduction in nocturnal hypoglycemia.)

Another potential advantage for real-world patients who switch from Lantus is Toujeo's greater length of action. The older medication barely lasts 24 hours, so patients must inject themselves promptly or risk high blood sugar. Toujeo's (as yet untested) longer action will theoretically improve outcomes by protecting occasionally tardy users from themselves.[15]

Afrezza's trial performance suggests that it, too, may benefit real-world patients in subtle ways that Sanofi cannot advertise, but its main selling point is obvious to anyone who has ever endured an injection. While research indicates that needles rank among the biggest barriers to treatment compliance in diabetic patients,[16] opinions vary wildly about the market for alternatives that are inhaled rather than swallowed.

Some wonder who wouldn't want to inhale medication rather than inject it. Others say that the failure of Pfizer's Exubera proves the answer is "nearly everybody." (Pfizer lost $2.8 billion on the product before pulling it from the market in 2007, just a year after launch. Its reception was so brutal that large drug companies abandoned all work on inhalable insulin. Afrezza was developed by a much smaller firm called MannKind.[17])

"Exubera failed because it came via a large and odd-looking device that was hard to carry and embarrassing to display. If you took the thing out at a restaurant to get some insulin before you ate, people might turn and stare because it looked like you were smoking pot from some sort of unique bong," said Mark Peyrot, PhD, a sociology professor at Loyola University of Maryland, in an interview with *EBDM*. Peyrot studies the psychological aspects of diabetes.

"Afrezza is totally different. The device it comes in looks like an inhaler that is used to deliver asthma medication," Dr Peyrot told *EBDM*. "I'm not predicting this single improvement guarantees it will become a blockbuster, but there's no reason to think Exubera's performance dooms it."

To the contrary, Peyrot thinks that many patients yearn for an injection replacement (that doesn't look like a bong) and that the new delivery system may significantly increase the wilingness of its users to take rapid-acting insulin with meals. "Only a small percentage of people are truly terrified of injections, but many feel some visceral aversion to them, and that's only the beginning of the problem," Peyrot said. "People find needles embarrassing and don't want to inject themselves with a needle in front of others, so they often find themselves doing it in toilet stalls, which are the last place on earth they want to use something that's supposed to be sterile. Besides, injections can hurt."

Despite the previous failure of inhalable insulin, there is some evidence—in the track record of insulin pens—that alternative delivery systems can attract large numbers of uses and improve insulin adherence. Insulin pens improve upon vial-syringe-needle systems in a wide variety of ways. They provide users with a quicker and more discreet way to inject themselves. They're easier to carry around. They improve dosing accuracy. They eliminate the need for injection technique. They even tend to hurt less. These advantages have attracted significant user numbers in almost every wealthy country around the world—except for the United States, where their adoption among insulin users may still be under 10%.[18]

People who do try pens tend to prefer them. More importantly, pens seem to promote treatment adherence. A study of more than 1800 patients concluded that use of one company's pen (rather than a syringe) was associated with a 39% greater odds ratio (OR) of maintaining a medication possession ratio of 0.80 or higher over a 12-month follow-up period (OR, 1.385; 95% CI, 1.037-1.849).[19] A recent review of compliance research found 4 pen-user studies, all of which reported significant compliance benefits.[20]

And pen design keeps improving. Sanofi said the pen that comes with Toujeo requires less application force and less hold time than the model that comes with Lantus.

Such incremental improvements seem unlikely to change patient behavior as much as the transition from injector to inhaler, but it's still unclear what impact, if any, that transition will have. Afrezza hasn't been on the market long enough for anyone to study its effects in real-world usage.

Sanofi and MannKind are planning post launch research, however, because any evidence that Afrezza significantly increases adherence and outcomes will surely boost sales and justify the product's considerable price premium: $7.54 per day compared with $3.14 for Apidra.[21] (The effective price premium for Toujeo remains unclear, as the drug retails for the same price as Lantus, but Lantus biosimilars have yet to hit the US market and begin price competition.[3])

Even after real-world performance data do become available, the cost-effectiveness of the new drugs may remain unclear. Experts still argue about whether actual health benefits justify the price we pay for Lantus and other analogue insulin formulations that have been around for many years. Some say there's little evidence that the (relatively) new products control blood sugar any better than far older products and argue that their few indisputable advantages, like the reduced chance of hypoglycemia, could be duplicated via strategies that cost billions less, like having a snack before bed.[22]

Others argue that the benefits of analogue insulin treatments tend to be hard for trials to measure. For example, analogue formulas can save patients several shots per day, which boosts compliance in real life but not in trials. Analogues also hold blood sugar levels much steadier than human insulin, which has no effect on A1C reduction but may prove a major long-term benefit.[23]

Experts may still be having the same argument a decade from now, but assuming that no one discovers an actual cure for both types of diabetes, the slow but steady parade of new treatment options will continue, offering hope to both physicians and analysts. **EBDM**

"I've been hesitant to be too much of a cheerleader for Afrezza, because I thought maybe I was experiencing beginner's luck—the thrill of any shiny new diabetes treatment can wear off pretty quickly—and given how controversial this drug is, I didn't want to stir the pot unnecessarily.

But sorry Naysayers, Afrezza is the bomb. At least for me."

—**Amy Tenderich**, Founder and Editor, *Diabetesmine,* April 22, 2015.

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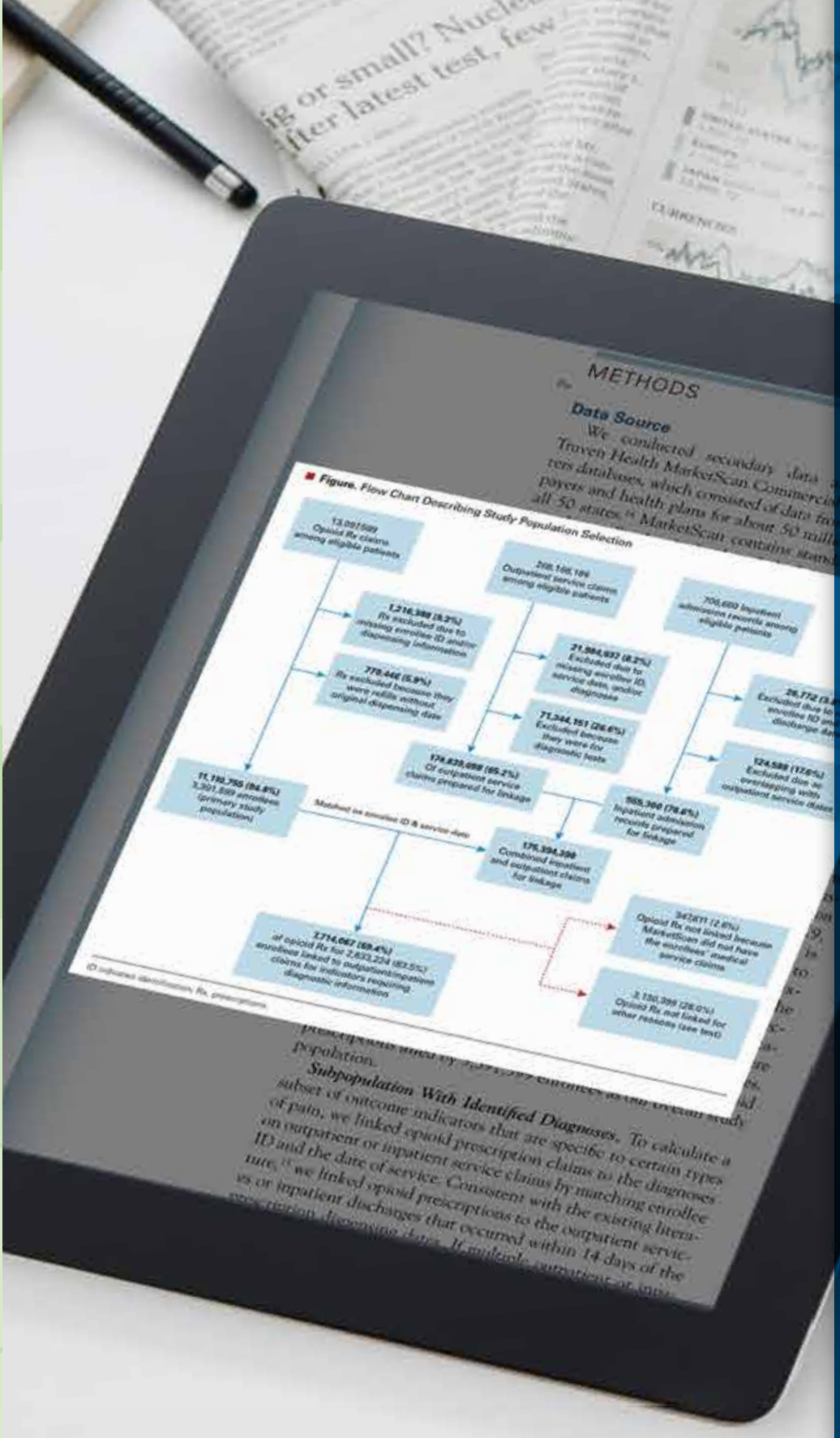

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PROMISE Results Have Implications for Managed Care; May Change Guidelines, Put Pressure on Payers to Cover CTA

Mary K. Caffrey

PAMELA S. DOUGLAS, MD

"No one's done a clinical outcomes study of this size on imaging," said Douglas, of Duke University. Findings in the PROMISE study would elevate CTA from a "maybe" to a "definitely appropriate" in clinical guidelines, she said.

DANIEL MARK, MD

CTA had presented the opportunity to "see" inside arteries, a holy grail doctors had hoped for until fears arose about overuse of tests. Mark, of Duke University, said that hasn't happened, and CTA is superior for predicting which patients need more procedures.

Patients who had computed tomography angiography (CTA) to evaluate their symptoms of heart disease fared about as well as patients who had functional testing for coronary artery disease (CAD), according to results of a large, federally funded trial presented March 14, 2015, at the 64th Annual Scientific Sessions of the American College of Cardiology.

The PROMISE study, one of the highlights of the meeting in San Diego, California, won praise from some for its "real world" focus, but also generated criticism for revealing the extent to which heart scans expose patients to radiation.

Both the study's lead author and an editorial in the *New England Journal of Medicine*,[1,2] which simultaneously published the results, predicted updates to clinical guidelines—and perhaps pressure on payers to cover CTA. A companion economic study showed that CTA isn't the healthcare cost-driver that some feared. This is good news, since 4 million Americans with health profiles similar to those in the study need tests each year for mid-range symptoms of heart disease. The *NEJM* editorial declared, "The cardiovascular imaging field is delivering comparative effective studies with results that are likely to change clinical practice."[2]

PROMISE stands for Prospective Multicenter Imaging Study for Evaluation of Chest Pain. Top-line data for both the clinical and economic results were outlined together at a press conference, while the full studies were presented at separate late-breaking sessions. The National Heart, Lung, and Blood Institute funded the study, which cost $40 million, according to the Associated Press.[3]

From a managed care standpoint, results of the PROMISE trial are groundbreaking on several fronts. "No one's done a clinical outcomes study of this size on imaging," said Pamela S. Douglas, MD, of the Duke Clinical Research Institute, lead author of the clinical study. She predicted the findings will elevate CTA from a "maybe" to a "definitely appropriate" for physicians in clinical practice.

The study combines clinical findings with an economic analysis, which will be important for payers and policymakers. Daniel Mark, MD, also of the Duke Clinical Research Center, in presenting the economic data, said that CTA at the 2-year mark increased overall costs by less than $500 per patient, and the procedure "allows a more efficient use of downstream catheterization," than functional tests.[4]

However, Eric Topol, MD, of the Scripps Clinic in La Jolla, California, posted a critique of the *NEJM* editorial on Twitter and later told the Associated Press that the findings were "a bad reflection on American medicine" due to the radiation exposure patients received.[3]

The study involved 10,003 patients with no prior diagnosis of coronary artery disease (CAD) but with symptoms that made physicians suspect heart disease, such as chest pains or shortness of breath. Almost all had a risk factor associated with CAD, such as diabetes, high blood pressure, or a history of tobacco use. Half were randomly selected for CTA, which gives physicians a view of the arteries to determine whether they are narrowing. The others took an electrocardiogram (EKG), echocardiogram (ECG), or nuclear stress test; each of these tests evaluates the heart's response to a stimulus. PROMISE represents the first time these 2 common tests have been compared head-to-head, an important milestone since current guidelines do not give either test priority.

Clinical Findings. The mean age for patients was 60.8 years, and 52.8% of patients were women. Over a mean follow-up of 25 months, a primary end point—a composite of death, myocardial infarction, hospitalization for unstable angina, or major procedural complications—occurred in 164 of the 4996 patients (3.3%) who received CTA. Among patients receiving functional testing, the primary end point occurred in 151 of the 5007 patients (3.0%) who received exercise EKG, nuclear stress testing, or stress ECG. The vast majority of the patients in this group (67.3%) received nuclear testing, with 22.5% receiving stress echocardiography and 10.2% receiving exercise ECG. The difference in clinical outcomes between the 2 strategies was not statistically significant.

Some reporters questioned whether any positive conclusions could be drawn from these results, but both Douglas and Mark said that would be taking a narrow view. There were many results from the trial that researchers did not expect to see, such as the very low rate of cardiac events. Douglas pointed out that patients who had CTA were more likely to take medications that controlled the number of cardiac events.

Economic Findings. Mark explained that for cardiologists, the arrival of CTA presented a holy grail they had always hoped for—the opportunity to "see" what is happening in the arteries. And yet as the technology was being developed, he said, "Some of us have had second thoughts whether that's such a good idea." Would CTA end up being an expensive, overused technology that would lead to unnecessary radiation exposure and downstream costs, as physicians pursued additional testing of uncertain findings that turned up in this diagnostic test? Or would CTA lead to precision care, with only those needing revascularization opting for the procedure?

Such fears, as well as concerns about radiation exposure, have led to lukewarm reviews of CTA in clinical guidelines and among payers, although Mark noted that even among the functional tests, doctors in PROMISE overwhelmingly chose the high-tech, higher cost nuclear test option. Experts on hand noted that improvements to CTA are reducing the level of radiation exposure that patients experience.

Mark's data estimated the overall cost of a CTA test at $404. For the functional tests, the cost of ECG with an exercise stress test was $514, while the cost of ECG with a pharmacologic stress test was $501. The estimate of a nuclear test was $946 and an exercise and pharmacologic stress testing was $1132. An ECG was the least expensive, at $174.

CTA increased the use of invasive catheterizations by 4% over functional testing, and those in the CTA arm were twice as likely to have revascularization. However, Mark noted that as experts predicted, CTA does appear to do a better job of correctly identifying those patients in need of additional procedures: 51% of the CTA patients referred for catheterization underwent revascularization compared with just 39% of the functionally studied patients. In addition, fewer patients referred for catheterization via CTA were found to be negative for obstructive disease compared with those referred via a functional test—an important point, because reducing unnecessary invasive tests is receiving increased scrutiny. **EBDM**

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PEGASUS Trial Shows Long-Term Benefits of Ticagrelor After Heart Attack

Mary K. Caffrey

Patients who took ticagrelor with aspirin for an extended period after suffering a heart attack were less likely to die later from cardiovascular causes, heart attack, or stroke, according to results presented March 14, 2015, at the 64th Annual Scientific Session of the American College of Cardiology, held in San Diego, California.

The results, simultaneously published in the *New England Journal of Medicine*, were reported from the PEGASUS-TIMI 54 trial, which involved 21,162 patients at more than 1000 sites in 31 countries. All had experienced a heart attack in the previous 1 to 3 years and had at least 1 other factor, such as diabetes or advanced age, that put them at risk of a second heart attack.

The trial's full name is Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54. Patients in the trial were randomly assigned a twice-daily regimen of ticagrelor—at 90 mg or 60 mg—or placebo, in addition to low-dose aspirin. Efficacy was virtually the same with both doses, according to Marc S. Sabatine, MD, MPH, senior physician in the Cardiovascular Division at Brigham and Women's Hospital and Harvard Medical School, Boston. Sabatine presented the results at the late-breaking session and afterward at a press conference.

Image courtesy of AstraZenca

Ticagrelor is a dual antiplatelet therapy currently prescribed for patients with acute coronary syndrome. Sabatine said that in tracking the number of cardiovascular events that patients experienced, the "event curves" between patients taking the drug with aspirin and those taking aspirin alone continued to widen each month up to the 1-year mark, suggesting that there might be a continued benefit after that point. The question, however, was whether the dose patients needed 2 hours after a heart attack would still be needed 2 years after a heart attack. "That was the basis for our trial," he said.

The patients' mean age was 65 years, and 76% were male. The average time since patients had suffered a qualifying heart attack was 1.7 years. Results showed that both doses of ticagrelor reduced the likelihood of cardiovascular death, heart attack, or stroke, which was the study's primary end point. There was a 15% reduction among those who had the 90 mg dose and a 16% reduction for those receiving the 60 mg dose, compared with those receiving placebo. Patients were followed for an average of 33 months.

"The benefit we saw was remarkably consistent across the individual components of the end point and in all the major subgroups of patients," Sabatine said.

Many questions arose about ticagrelor's effect on bleeding. In the data and in remarks at the press conference, Sabatine drew distinctions between fatal events or intracranial hemorrhage and less serious events, including those that might require hospitalization. Rates of TIMI major bleeding were higher with ticagrelor (2.60% with 90 mg and 2.30% with 60 mg) than with placebo (1.06%), with $P < .0001$ for each dose vs placebo. For rates of intracranial hemorrhage or fatal bleeding, however, rates for all 3 groups were about the same: 0.63% for the 90mg dose, 0.71% for 60 mg, and 0.60% for placebo.

While taking questions during the late-breaking session, Sabatine suggested that while a 90mg dose of ticagrelor is called for immediately after a heart attack, dropping down to a 60 mg dose at the 1 year mark may make sense, due to the findings about efficacy, bleeding, and side effects.

Patients taking the drug also experienced more shortness of breath. About 7% of patients discontinued the drug due to bleeding and about 5% stopped taking it due to shortness of breath.

Valentin Fuster, MD, PhD, of Mount Sinai Hospital and editor of the *Journal of the American College of Cardiology*, commented that the ticagrelor results are part of "an evolving trend of using long-term dual anti-platelet therapy." The benefits seen must be weighed against the instances of bleeding and shortness of breath, Fuster said, adding that each physician must use his or her own judgment given the profile of the individual patient. "I think we should be a little bit cautious," he said. **EBDM**

Ticagrelor is made by AstraZeneca, which sponsored the trial.

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Cholesterol-Fighting Drug Evolocumab Also Reduces Cardiovascular Events, Study Finds

Mary K. Caffrey

The much-anticipated PCSK9 inhibitor evolocumab, already shown to have dramatic effects on lowering low-density lipoprotein (LDL), or "bad" cholesterol, has now been shown to reduce the likelihood that patients using the drug will suffer a heart attack or stroke, or need a procedure to open blocked arteries, and thus may reduce mortality.

The study on cardiovascular (CV) effects was presented March 15, 2015, at a late-breaking session and press conference of the 64th Annual Scientific Sessions of the American College of Cardiology (ACC). Attendees came early to the packed session in San Diego, California, much as they did the year before when the drug's cholesterol-fighting powers were revealed at ACC in Washington, DC.[1] Results were simultaneously published in the *New England Journal of Medicine*.[2]

The ACC session offered a backdrop for the race to the FDA finish line between Amgen and Sanofi-Regeneron over PCSK9 inhibitors.

Evolocumab, an injectable drug that can be given either once or twice a month, is Amgen's entrant in the race to see who will be first to win FDA approval for this new class of therapy, the PCSK9 inhibitors. (Amgen funded the study presented in San Diego.) The wait for evolocumab and Sanofi-Regeneron's counterpart, alirocumab, has been called the most-anticipated pharmacy event of 2015. Both companies were highly visible in San Diego, with educational presentations about the monoclonal antibody that inhibits PCSK9, or proprotein convertase subtilisin-kexin type 9.

Pharmacy industry experts who spoke with *The American Journal of Managed Care* earlier this year predicted that this new class of cholesterol fighters will be a blockbuster, but could significantly raise costs in a therapeutic area where most patients have long relied on low-cost statins. In the press conference after the late-breaking session, Marc Sabatine, MD, MPH, senior physician in the Division of Cardiovascular Medicine at Brigham and Women's Hospital, Boston, deflected questions about cost.

"I don't view these as potential competitors to statins," Sabatine said. "Statins are the foundation." However, he said, patients who can benefit from evolocumab include those who cannot tolerate statins, those who cannot achieve a sufficiently low LDL-cholesterol count on current therapies, and patients with a rare condition called familial hypercholesterolemia. (This condition has played a role in the race between Amgen and Sanofi-Regeneron.)

Clinical Findings. In 2 open-label, randomized trials, researchers enrolled 4465 patients who had previously taken part in phase 2 or 3 studies of evolocumab. Patients were randomized 2:1 to receive the study drug in either a 140mg dose every 2 weeks or a 420 mg dose once a month, plus standard therapy, or standard therapy alone. Patients were followed for a median of 11.1 months. Lipid levels, safety, and adjudicated CV events were recorded and data from the 2 trials combined.

Compared with standard therapy alone, evolocumab reduced LDL cholesterol 61%, from a median of 120 mg/dL to 48 mg/dL (P <.001). The rate of CV events at 1 year was reduced from 2.18% in the standard therapy group to 0.95% in the evolocumab group.

Adverse events (AEs) were similar in both groups, although neurocognitive events were more frequently reported in the evolocumab group; the issue of neurocognitive events has already caught the attention of the FDA. Authors reported that the risk of AEs did not vary significantly with decline in LDL cholesterol. A trial of 27,500 patients to determine long-term cardiovascular outcomes and side effects is under way, with results expected in 2017.

Vying for First-in-Class. Multiple published reports have chronicled the heated race between Amgen and Sanofi-Regeneron to be the first to win FDA approval for a PCSK9 inhibitor.[2,3] Since 3 studies on evolocumab were presented a year ago, both Amgen and Sanofi-Regeneron have taken aggressive steps to be the first in this class to reach consumers.[1-3]

MARC SABATINE, MD, MPH

The Brigham & Women's physician said statins remain the "foundation" for lowering LDL cholesterol, but that a medical need exists for patients who cannot tolerate statins or whose cholesterol remains high despite therapy.

On January 26, 2015, Sanofi and Regeneron announced that they had filed alirocumab for priority review, following the purchase of a $67.5 million voucher from BioMarin, which the company received for its development of a pediatric drug for Morquio A syndrome. Vouchers can be sold or transferred, and the Sanofi-Regeneron purchase is linked to alirocumab's potential to aid patients with familial hypercholesterolemia. The purchase gives the FDA until July 24, 2015, to approve or reject the drug.[3] Amgen, meanwhile, sued Sanofi and Regeneron in a US District Court on October 17, 2014, charging patent infringement.[4] The FDA deadline for Amgen's evolocumab application is August 27, 2015.

Sabatine faced tough questions from the press about which patients will take evolocumab and for how long, given the speculation about its possible cost. He said pricing issues were up to the manufacturer. "Typically, the indication for LDL cholesterol populations is determined by guidelines and by payers," he said, adding that it was important to consider those patients "who have unmet medical need."

He went on to discuss the possibility that medicine has not fully considered the potential to dramatically lower LDL cholesterol in patients for whom only modest reductions are currently possible. "When we think about how much we should lower LDL, we haven't found a floor beyond which we haven't found a benefit," he said. However, he acknowledged that the use of PCSK9 inhibitors would come down to a balance, based on each patient's medical need and what cost payers were willing to bear.

An accompanying editorial in *NEJM* acknowledged the excitement over the results for patients who do not tolerate statins or have hard-to-lower cholesterol. However, the writers urged caution about using intense therapy to lower LDL cholesterol for most patients, when there are options available with well-established safety records.

"The evidence-driven cholesterol guidelines did not endorse the concept that lower LDL cholesterol levels are better at all costs," wrote Neil Stone, MD, and Donald Lloyd-Jones, MD. The guidelines emphasized that, "while lower is better, it matters how you get there and whether the benefits outweigh the risks for that patient."[5] **EBDM**

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Session Offers Cardiologists Insights Into New Payment Models, ACOs

Mary K. Caffrey

The Affordable Care Act (ACA) brought with it a host of provisions to change the way healthcare is delivered, all designed to make Americans healthier while making the system more accountable and less costly. Because cardiologists are more affected by these changes than most specialists—their patients tending to be older, sicker, and more reliant on Medicare—there is pressure on them to change the way they do business.

To teach cardiologists how to respond to new payment models, the 64th Annual Scientific Sessions of the American College of Cardiology, held in San Diego, offered a March 15, 2015, session titled "Transforming Care: Innovations in Delivery and Payment Systems for Cardiovascular Care."

Michael E. Chernew, PhD, professor of healthcare policy at Harvard Medical School and co-editor-in-chief of *The American Journal of Managed Care*, offered a policy overview to help cardiologists understand the forces behind new payment models, in particular accountable care organizations (ACOs). Because of federal fiscal concerns, it is important to understand that the policy discussions surrounding payment reform are often motivated less by health and more by taxes, Chernew said, as policy makers seek to stem healthcare's unsustainable share of federal spending.

Payment reforms represent one strategy to control spending growth, and one type of payment reform is simply to pay less, he said. But there is more enthusiasm for developing a payment approach that moves away from the traditional fee-for-service (FFS) model and toward a system that bundles care across time and provider type. (For example, CMS recently announced that 30% of Medicare payments will need to be tied to value by 2016, and 50% by 2018.) Examples of such reforms include payment bundles for episodes of care and global payments for each patient.

An important step in the transition has been the creation of ACOs, which are healthcare systems that take responsibility for patients at all levels of care, while giving these systems opportunities to share in savings if they produce better than expected outcomes for their patient populations. While Chernew presented data showing significant ACO growth among Medicare ACOs, commercial insurers have also pursued risk-sharing models. As he explained later in the question-and-answer session, a challenge with ACOs is that while they are supposed to ensure coordination of care, it may not be in their interest to form direct relationships with post acute elements like

skilled nursing facilties if the incentives are not in alignment.

ACOs were designed to slow spending growth, and Chernew presented data that showed this is happening for cardiologists. But ACOs have their problems, including patients not staying with the same ACO from year to year, or seeking care from non-ACO providers during the year. Another challenge is that currently, ACO payment is based on organization-specific performance, meaning that successful ACOs see a greater drop in benchmarks over the contract period. This discourages savings. Chernew noted CMS is likely to reform this part of the program in the future.

Andrew Ziskind, MD, a cardiologist and health system administrator now with Huron Consulting Group, Chicago, Illinois, discussed the specialty's challenges due to its older patient population, whose costs run much higher than those of their European counterparts. Later, during the question-and-answer period, he elaborated on how this is largely due to American cultural differences that push medicine toward costly end-of-life care even when positive outcomes are unlikely. He subsequently called on fellow cardiologists to embrace and promote palliative care, an option which studies show is widely embraced by patients.

Controlling costs in the era of bundled payments, he said, will demand better management of outpatient care. As Chernew mentioned before him, trends toward consumerism—happening in part because cost-sharing is being pushed down to patients—mean that individual patients will have access to information about the price of tests and procedures that they would not have thought to ask for in the past.

The fundamental shift from FFS to payment for value is going to create more risk for providers, especially the government, which becomes a larger "payer" in the healthcare system.

Competition on price will come down to what is happening locally, Ziskind said. "We can talk about national trends, but the local market, each local metro area, is different." How much provider competition is there? What is the relationship with the hospital? Most critically, what is the culture of utilization: is it like the Northwest, with a culture of low utilization, or more like New York and Florida?

Shared savings will continue to be a force for change, he said, but it has a bottom. "The cost of care can't go down to zero," he said.

A key criterion for contractor relationships between providers and payers in the near term is, what are the exclusion criteria that allow payment to revert to fee-for-service? This is important to specialists.

Most of all, Ziskind encouraged cardiologists to become engaged in payment reform within their institutions, build better infrastructure, and demand a seat at the table. Cardiologists need to look for areas where they can help the systems they are in to improve, especially in chronic disease management. Tomorrow's rewards will come from avoiding unnecessary costs. "You want to be preparing for the future. Protect your fee-for-service revenue, but at the same time, be preparing for the future," Ziskind said. "If we as cardiovascular providers can do a better job of delivering care, the economic alignment is there."

Cathleen Biga, CEO of Cardiovascular Management of Illinois, said the recent past has been a time of change in her organization. "When we left this conference 2 years ago we knew we had to do something," she said. Navigating the transition from FFS to bundled payments is very difficult for providers, because "If you arrive too soon you might be penalized, and if you arrive too late you might be penalized."

There's no rule book, Biga said, "except the colleagues I call on a routine basis."

CMS' Center for Medicare and Medicaid Innovation has models for acute, acute/post acute, and post acute care, and like Ziskind, Biga recommends that post acute care is where a health system's focus has to be. Yet for cardiologists this represents a true change of mind-set, because many practitioners have spent careers performing procedures that had little to do with outpatient care. Today, Biga pays attention to what happens in nursing homes, because so much of a bundled payment can be consumed in that setting.

Cardiology, she said, is not a specialty like, for example, orthopedics, where a patient is treated, healed, and sent on his way. When a patient is diagnosed with cardiovascular disease, "You are part of our world forever." This has meant "blowing up" a delivery of care model that Biga said "pigeonholed" caregivers. "We were not good at transitions of care." It was hard to do but essential. Her organization worked with a convener, gathered tons of data, and had to learn to manage "this little thing called risk."

Along the way came some interesting discoveries: it made more sense to keep a patient in the hospital an extra day than to send him to a nursing home and risk triggering a series of recertifications that would drive up costs. Cardiologists had to develop better relationships with hospitalists who controlled patients' care. And the big one—especially in the Chicago area—has been gaining control over decisions about which nursing homes receive discharged hospital patients and ensuring that they receive quality care.

Details matter, Biga said. Paying attention to documentation and coding is essential. "The office is just as important to risk adjustment," she said. "If you've got a sick, chronic patient, document it." **EBDM**

MICHAEL E. CHERNEW, PHD

The Harvard expert in health economics and co editor of *The American Journal of Managed Care* said consumers are gaining more information about the prices of tests and procedures, data they would not have sought in the past.

Hospitals in Low-Income Areas Scored High in MI Care, Even if Patients Had Poor Outcomes

Mary K. Caffrey

A study presented March 16, 2015, at the 64th Annual Scientific Session of the American College of Cardiology (ACC) found that the quality of the care for myocardial infarction (MI) was just as good if not better in hospitals serving low-income areas than elsewhere in the United States, even if those standards were not always reflected in patient outcomes.

The results could have policy implications, as CMS moves to tie Medicare reimbursement to readmission rates and patient outcomes. The study attaches data to a complaint raised by hospitals that serve the poor: strict attention to outcomes without accounting for how long-term poverty affects health will cripple those institutions that most need federal dollars.

"Despite getting good care, some patients may be prone to poor outcomes," said Jacob A. Udell, MD, MPH, of the Women's College Hospital and Peter Munk Cardiac Centre, University of Toronto. He presented the study "Socioeconomic Disparities and Quality of Hospital Care after Myocardial Infarction in A National Cardiovascular Data Registry" on March 16, 2015, in San Diego, California.

Many institutions affected by CMS' reimbursement policies are academic medical centers that train physicians; if current policy trends continue, Medicare penalties will affect medical education programs. Changes are deeply felt in cardiovascular care, because CDC statistics show poverty is associated with higher rates of diabetes, obesity, and tobacco use, all of which affect the ability to survive a CV event. These are the patients that many academic centers treat, in what Udell called the "risk-treatment paradox."

"Patients who will be the worst off get the best care in teaching hospitals, because they do a great job with acute management," he said.

Udell and his coauthors took a unique approach, one made possible by the rise of quality metrics reporting: pairing data from the ACC Foundation's National Cardiovascular Data Registry (NCDR) and overlaying the MI quality scores for 390,692 cases with socioeconomic measures based on US Census data collected by zip code. (Use of zip code data as a proxy for individual wealth is a demographics measurement method of long standing.)

Specifically, researchers used data collected between July 2008 and December 2013 in a hospital registry that is part of ACC NCDR. Researchers looked at 6 quality measures during the acute phase of MI care and 6 different quality measures

at discharge. For the analysis, researchers divided the hospitals into quintiles based on the socioeconomic data of their patient populations. Notably, there was greater separation from the lowest to highest quintile by average housing value—$58,450 to $156,900—than there was by income, where the averages in the lowest and highest quintiles were $27,086 and $57,317, respectively.

Data revealed that hospitals in the lowest income quintile neighborhoods served patients who smoke, who were least likely to have private insurance coverage, and who were most likely to have diabetes. These results reflect CDC statistics that show 29.2% of adults who are below the poverty level smoke, compared with 16.2% of adults who are at or above the poverty level. Among adults under age 65 years, 30% of Medicaid enrollees smoke, compared with 15% of adults with private insurance.

Overall quality scores—which track how well hospitals performed procedures—were very close across all quintiles in the acute care phase. The lowest income quintile scored 91.0%, slightly better than the 90.2% scored by the highest income group. Scores for procedures at discharge were less favorable among all groups, and this area has been a target of CMS. In this area, overall scores for the lowest income group lagged 70.0% to 76.7% for the middle-income group, which scored highest.

JACOB A. UDELL, MD, MPH

The cardiologist from Women's College Hospital, University of Toronto, said his group's findings are important in light of CMS policies to penalize hospitals with higher mortality rates, without factoring-in patients' underlying health.

Even though hospitals in the lowest income areas were adhering to quality standards, in some cases better than counterparts in wealthier areas, overall mortality rates were higher than in most other quintiles (although lower than in the highest-income hospitals). Hospitals in the poorest areas had particularly high mortality rates due to heart failure or bleeding compared with death rates from MI itself.

Low scores on discharge performance by hospitals in the poorer areas will attract CMS' attention. Reformers behind accountable care organizations, which take responsibility for patient health on an ongoing basis, would ask academic centers what they can do with community groups to promote continuity of care for their populations. However, not all lower-income Americans have gained access to coverage under the Affordable Care Act; the study showed that the largest number of institutions serving the poor was in the South, where several states have not expanded Medicaid.

A limitation of the study, which drew attention from commentators at the ACC session, was the 17% of patients who could not be analyzed because of missing or incomplete data for the socioeconomic analysis. However, Udell noted that the distribution was random; as a practical matter, this is still the type of data CMS uses to make policy decisions on Medicare.

The good news, the study concluded, is that quality initiatives appear to be working. Hospitals taking part "appear to provide equitable in-patient care to individuals living in the most disadvantaged neighborhoods compared with the rest of the nation," researchers concluded. **EBDM**

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Losing Weight—And Keeping it Off—Can Free Patients From Atrial Fibrillation

Mary K. Caffrey

Maintaining weight loss offers many health benefits, and a study presented on March 16, 2015, at the 64th Annual Meeting of the American College of Cardiology added another item to the list: obese patients with atrial fibrillation are far more likely to rid themselves of this heart ailment if they shed pounds.

For obese patients, weight loss might require support, as researchers of the LEGACY (Long-Term Effect of Goal-Directed Weight Management on an Atrial Fibrillation Cohort) study concluded. Support is worth providing, because the study found that if patients lost at least 10% of their body weight, they were 6 times more likely to achieve arrhythmia-free survival.

The study, led by Rajeev Pathak, MD, a cardiologist and fellow in electrophysiology at the University of Adelaide, Australia, was the first study to outline the benefits of sustained weight loss, the effects of the amount of weight lost, and the impact of changes in weight over time among patients who suffered from atrial fibrillation (AF). This condition causes shortness of breath and muscle weakness, and can indicate stroke risk. Treatment typically includes anticoagulants, which can present their own risks in some patients.

"We found that sustained weight loss is achievable in obese patients and that it can significantly reduce the burden of atrial fibrillation," Pathak said. Previous studies had examined only the short-term effects of weight loss on AF.

LEGACY researchers enrolled 355 participants in a weight loss clinic that provided support through 3 in-person visits a month, nutrition guidance, exercise, counseling and a physical activity diary. All participants were obese (with a body mass index of at least 27 kg/m^2) and had AF at the start of the study, and all agreed to participate, which Pathak acknowledged does pose some limitations to the results. Subjects with permanent AF, previous AF ablation, and severe medical illnesses were excluded.

Each year for 4 years, participants reported for a health exam and an assessment of their AF symptoms, based on their own reports and 7 days' worth of readings from a Holter monitor. Patients also underwent an echocardiogram and sonogram to measure heart health.

As subjects progressed, they were categorized based on the percentage of body weight lost. Researchers also tracked patients' AF symptoms, and the results showed that the burden of the condition decreased far more for those who lost the most weight, with both *weight loss* and *weight fluctuation* being independent predictors of outcomes. At the 4-year mark, 45% of patients who lost at least 10% of their weight, and 22% of those who lost 3% to 9% of the weight, were free of AF symptoms—without the need for surgery or medication. By contrast, only 13% of patients who lost less than 3% of their weight were symptom-free without such treatments.

RAJEEV PATHAK, MD

"We found that sustained weight loss is achievable in obese patients and that it can significantly reduce the burden of atrial fibrillation."

Both sustained weight management and an absence of weight fluctuation were associated with an absence of AF symptoms. Those who lost and regained more than 5% of weight between annual visits were twice as likely to experience symptoms. Stable weight loss also helped patients achieve improved blood pressure, cholesterol, and blood sugar levels. **EBDM**

The study was simultaneously published in the Journal of the American College of Cardiology.

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Moving to a Population-Based Approach to Find Links Between Diabetes, Heart Disease

Mary K. Caffrey

Connections between diabetes and heart disease are well known, but figuring out exactly which patients with diabetes will develop conditions such as congestive heart failure or cardiovascular disease is less straightforward. Can tools such as biomarkers or imaging help physicians? And how can moving away from "disease-based" to a "population-based" approach to identifying at-risk diabetics, especially women, play a role?

Speakers at the symposium, "Imaging the High Risk Diabetic Patient," represented a collaboration among several professional associations and the American College of Cardiology (ACC). It was held March 14, 2015, during the 64th Annual Scientific Sessions in San Diego, California.

Matthew J. Budoff, MD, of the University of California at Los Angeles, started the discussion by looking at how genetics is broadening medicine's understanding of the connections between diabetes and heart disease. He offered the caveat that diabetes risk is influenced by a mix of genetics, environmental factors, nutrition, and whether a person is obese. The vast majority—92% of patients—have insulin resistance, and many develop hypertension. The role that inflammation plays, inflicting damage at both the microvascular and macrovascular level, is key: according to Budoff, it appears that inflammation sets in motion the process that leads to cardiovascular disease.

Budoff discussed markers related to inflammation. The C-reactive protein, which is found in blood plasma and rises in response to inflammation, is a relatively weak marker, yet it is still associated with diabetes. Plasma levels tend to drop in patients with diabetes, also in response to inflammation.

Finding good markers is important, Budoff said, because "There is a rising tide of cardiovascular disease in diabetes," that is hard to explain, even with the rise in diabetes itself.

Robert S. Rosenson, MD, of Mount Sinai Hospital in New York City, noted the weaknesses of current risk assessment tools: most are based on information reported by patients themselves, and have been developed across a diverse set of populations worldwide. It's widely recognized that assessment tools that work with 1 population are not transferable to another population with a different ethnic background, diet, or culture.

Experts who spoke at a symposium during the 64th Scientific Sessions of the American College of Cardiology said that figuring out which patients with type 2 diabetes mellitus are also at risk for cardiovascular disease is not straightforward.

Studies of the components of metabolic syndrome are pointing toward potentially valid ways to connect risk scores between different conditions. There's been debate about glycated hemoglobin (A1C) and cardiovascular disease (CVD), and those relationships are quite striking, Rosenson said. While evaluating several CVD risk prediction models, he cautioned that it's not a simple matter to apply them to a population with diabetes.

> *"This is risk-guided treatment. We are moving from the disease-centric model to the patient-centric model."*
>
> —REGINA DRUZ, MD

For example, a genetic-based tool for coronary artery disease (CAD) did not prove to be a dependable prognostic tool when applied to a diabetes population. New tools are needed that can take existing models and apply them across populations using known biomarkers, while taking ethnic differences into account, he said.

W. Guy Weigold III, MD, of MedStar Washington Hospital Center, said that while there is clearly a relationship between diabetes and heart disease, "a one-size-fits-all paradigm is not accurate." And this is particularly true when using imaging to test for calcium in persons with diabetes. For example, a calcium score would seem a straightforward biomarker. But while imaging can help, it's not a simple process, Weigold said. He reviewed several studies of this phenomenon, including a 2003 study by Wong, et al.[1] "Patients who had diabetes with metabolic syndrome have some degree of coronary calcium, but some of these patients don't have any calcium," he said. "Right off the bat, it's not necessarily the case that diabetes always equals coronary artery disease."

Diabetics also accumulate calcium differently, Weigold pointed out; their maximum calcium scores tend to reach a peak, while nondiabetics with heart disease have scores that tend to keep increasing gradually. Calcium scores can be used to stratify diabetics for treatment, but some diabetics still have higher mortality, even with calcium scores of zero.

Prem Soman, MD, of the University of Pittsburgh, found that routine nuclear imaging of diabetics for silent ischemia yielded very little benefit, while Vera Rigolin, MD, of Northwestern University, found that stress echocardiography provided excellent prognostic information, especially given how rapidly conditions can change for persons with diabetes.

Throughout the session, presenters took note of the different indicators and outcomes for men and women. Regina Druz, MD, of iVisitMD in Long Island, New York, said that ensuring better care for women will require a different way of identifying patients who are at risk of heart disease. The process has traditionally been screening, taking history, taking a patients' baseline, and hoping for early detection and treatment.

But today's model of population health, Druz said, calls for physicians to deploy a risk stratification model that identifies groups of patients who need care before cardiac events occur. Among persons with diabetes, that may involve biomarkers or calcium tests but also an analysis of environmental and nutrition factors that may affect certain groups of patients. "This is risk-guided treatment," she said. "We are moving from the disease-centric model to the patient-centric model."

New indicators will emerge for identifying patients, because even the 2013 guidelines from ACC and the American Heart Association don't offer cardiologists thorough information on risk assessment, Druz said, adding, "Everything boils down to identification of global CAD risk." As physicians learn more about the effects of genetics and other factors that propel diabetes to trigger heart disease, "this is a framework that will grow with us into the future." **EBDM**

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New Therapeutic Approach Did Not Reduce Scarring After Angioplasty

Mary K. Caffrey

C. MICHAEL GIBSON, MD

Gibson said that while the study showed Bendavia did not prevent irreversible heart injury, there was some evidence it may aid the heart pumping function, and this will be the topic of further study.

A drug designed to reduce tissue damage to the heart by targeting mitochondria in the cells did not work as researchers hoped for in a study presented March 15, 2015, at the 64th Annual Scientific Session of the American College of Cardiology, held in San Diego, California.

Patients who received Bendavia before undergoing a procedure to clear blocked arteries after a heart attack—either angioplasty or stent—showed no significant reduction in scarring compared with patients receiving placebo, according to results of the EMBRACE-STEMI study. Results were presented at a late-breaking session by C. Michael Gibson, MD, professor of medicine at Harvard and the study's lead author.

Among patients with STEMI (ST elevation myocardial infarction), injuries result when blood returns to the area that has been temporarily deprived of oxygen. The process causes the heart to pump blood even harder, which can result in further heart injury. The study drug, Bendavia, is a cell-permeable peptide designed to target cardiolipin, which is found in the inner mitochondrial membrane, to promote improved mitochondrial response during the process and limit the damaging effects of oxygen's sudden return to the tissue.

The study involved 297 first-time STEMI patients who were randomized to receive the drug (0.05 mg/kg/hr) or blinded placebo more than 15 minutes before a procedure to clear arteries. Patients receiving Bendavia showed a 10% reduction in scarring during the first 3 days after surgery, as measured by the levels of an enzyme called creatinine kinase-MB, the study's primary end point. However, this difference was not statistically significant. The results also suggested a trend toward improved heart pumping function during the 8 hours after patients received the drug, but that trend also did not reach statistical significance.

"Our study found that the drug did not prevent irreversible injury to the heart," Gibson said. However, the apparent sign that the drug reduced new-onset heart failure in the first hours after infusion may be an indication that Bendavia improves the heart pumping function and will be the subject of additional study, he said. The study's chief limitation was the small number of patients. **EBDM**

The trial was funded by Bendavia's developer, Stealth BioTherapeutics.

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Personal Coaching Halts Progression to Diabetes in Some Patients, Study Finds

Mary K. Caffrey

A comprehensive coaching program, which combined traditional elements like nutrition and exercise counseling with efforts to control stress and correct disrupted sleep, succeeded in reversing elevated blood glucose levels in nearly half the patients with prediabetes who took part. Results of the study, released March 5, 2015, by the American College of Cardiology (ACC), were presented during the 64th Annual Scientific Sessions held March 14-16, 2015, in San Diego, California. The study's lead author, Mariam Kashani, DNP, is chief scientific director at Walter Reed National Military Center, Bethesda, Maryland.

The study reports results of the Integrative Cardiac Health Project, which promotes healthy behavior to improve overall health and reduce cardiac risk. Researchers evaluated data for 508 consecutive participants, who were assessed for cardiovascular health and given personalized evaluations, featuring individual goals that met recognized preventive care guidelines. Of the participants, 107 had prediabetes, which meant their blood glucose levels were elevated, but not enough to be diagnosed with type 2 diabetes mellitus (T2DM). Prediabetes is defined as glucose >100 mg/dL and <140 mg/dL.

TABLE. Changes in Health Measures for Women Who Reversed Prediabetes

Risk Factor (n = 52)	Baseline	At 6 months	*P*
Fasting glucose (mg/dL)	105.4 ± 6.2	92.4 ± 5.4	<.001
Fasting insulin (IU/mL)	14.5 ± 10.1	10.4 ± 7.3	.02
Homestatic model assessment	3.8 ± 2.7	2.4 ± 1.7	.002
Total cholesterol (mg/dL)	190.7 ± 41.1	175.1 ± 39.0	.05
Low density lipoprotein (mg/dL)	115.8 ± 36.3	102.5 ± 34.7	.06
Systolic blood pressure (mm Hg)	134.3	127.9	.03
Body mass index (kg/m^2)	30.0 ± 5.7	29.0 ± 5.8	.40
Mediterranean diet questionnaire (14 points)	6.8 ± 2.4	9.2 ± 2.0	.002
Aerobic exercise time (minutes/week)	136.4 ±139.1	192.9 ± 161.7	.05
Perceived stress scale (56 points)	21.9 ±7.4	18.7 ± 7.0	.03
Pittsburg sleep index (21 points)	7.0 ±3.4	5.7 ± 3.7	.08
Fatigue score (10 points)	4.2 ±1.9	3.3 ± 2.0	.03

Source: Kashani M, et al. Presented at American College of Cardiology, March 14-16, 2015, San Diego, CA.

Participants then took part in 14 coaching sessions over a 6-month period, either in person or by telephone, with specialists in nutrition, exercise, sleep, and stress management. Researchers sought to measure the effect of the intervention on blood glucose levels and other risk factors.

Of the participants who had prediabetes, 49% were able to return their blood glucose to <100 mg/dL regardless of whether they lost weight, which the researchers found notable. On average, participants who were able to regain normal glucose metabolism lowered their fasting glucose level by 12%, dropping from 105.4 to 92.4 mg/dL. (See **TABLE**.)

"Many more patients reverted to normal blood glucose than expected, especially if we consider that they were not necessarily losing weight," Kashani said in a statement released by ACC. "This is important because prediabetes is a modifiable risk factor for cardiovascular disease."

The measurable reductions in blood glucose levels were significant, she said, because each 5 mg/dL reduction brings a significant reduction in cardiovascular risk. Patients with prediabetes also showed improvements in blood pres-

sure, fasting insulin, perceived stress levels, and adherence to a Mediterranean diet, and reported feeling less tired.

A major limitation is that the study was observational and had no control group. However, Kashani said those who were able to revert to normal blood glucose levels also had significantly lower triglyceride levels at 6 months compared with others who remained prediabetic. A study to compare this lifestyle intervention to usual care is under way, according to the ACC statement.

According to Kashani, the findings show that interventions must go beyond diet and exercise to include other factors. "By taking sleep and stress into account, we factor in important hormonal processes to better manage glucose," she said. "When we are stressed, our bodies release extra glucose and when we are tired, we tend to make poor food choices. In this context, people often regain weight, and in doing so, they may revert back to worsening blood glucose levels."

According to the American Diabetes Association, an estimated 86 million Americans have prediabetes, and 1 in 3 will develop T2DM within 5 years if elevated blood glucose levels are not addressed. Risk increases with a family history of diabetes, weight gain, and a sedentary lifestyle. **EBDM**

Reference

Kashani M, Eliasson A, Engler R, et al. Prediabetes reversal using a novel comprehensive health model. Presented at the 64th Annual Scientific Sessions of the American College of Cardiology; March 14-16, 2015; San Diego, CA.

Study of Heart Failure Patients Defines How Avoiding Risk Factors Can Add Years to Life

Mary K. Caffrey

How much does avoiding risk factors like obesity, diabetes, and hypertension in your 30s and 40s matter? A lot, it turns out. According to a study presented during the 64th Annual Scientific Sessions of the American College of Cardiology (ACC), persons who had all 3 risk factors by the age of 45 years were diagnosed with heart failure 11 to 13 years earlier than those without those risk factors.

Results of the study were released March 5, 2015, in advance of the annual meeting held March 14-16, 2015, in San Diego. The study also found that persons who had 1 or 2, but not all 3, of the risk factors developed heart failure an average of 3 to 11 years earlier that those without any of the risk factors.

Faraz Ahmad, MD, a Northwestern University cardiology fellow and the study's lead author, said the ability to quantify how much risk factors affect life span gives physicians a powerful message to bring to patients. "You really want to prevent or delay the onset of these risk factors for as long as possible," Ahmad said in a statement released by the ACC.

Heart failure means the heart cannot pump enough blood for the body to function properly. Once the condition is diagnosed, other health problems can multiply; patients can experience organ failure, fatigue, swelling, coughing, and wheezing. According to the ACC, about half of patients with heart failure die within 5 years of diagnosis.

To calculate how the onset of risk factors affects life-span, researchers pooled results from large studies that together covered 18,280 patients and spanned a total of 40 years: the Framingham Heart, Framingham Offspring, Chicago Heart Association Detection Project in Industry, and Atherosclerosis Risk in Communities studies. All participants were free of cardiovascular disease at baseline.

The researchers were able to identify 1449 heart failure events over 471,988 person-years of follow-up. Men and women without hypertension, obesity, or diabetes mellitus lived on average 35.3 and 37.0 years without heart failure, respectively.

Compared with the study subjects with no risk factors, those with hypertension, obesity, and or diabetes mellitus at baseline had fewer years of heart failure survival: 3 versus 11. Men and women without hypertension, obesity, or diabetes mellitus at age 45 years lived on average 11.3 to 12.7 years longer free of hypertension than those with all 3 risk factors.

Besides giving physicians powerful information for patients, Ahmad said the results would help policy makers and public health officials predict future heart failure prevalence as the US population ages. According to the CDC, 5 million people have the disease, which costs the nation an estimated $32 billion annually in healthcare services, medication, and missed days of work. **EBDM**

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Following Mediterranean Diet Cuts Heart Disease by Half, Study Finds

A study conducted in Greece found that closely following a Mediterranean diet offered more protection from heart disease than physical exercise, according to results reported in advance of the 64th Scientific Sessions of the American College of Cardiology (ACC).

The study, released March 4, 2015, added prevention of heart disease to the list of benefits that come with strict adherence to a diet emphasizing fruits and vegetables, whole grains, beans, nuts, fish, and olive oil. Adults who followed the diet were 47% less likely to develop heart disease over a 10-year period, compared with adults who did not follow the diet. According to a statement from ACC, this was the first study to track 10-year heart risk in a general population. Full results were presented at a poster session March 15, 2015.

The Mediterranean diet has previously been linked to weight loss and reduced risk of diabetes, hypertension, and elevated low-density lipoprotein (LDL) cholesterol levels.

Researchers did their study in and around Athens, Greece, because it is considered the home of the Mediterranean diet. However, they wrote that urbanization has caused many Greeks to adopt Western dietary patterns.

A sample of more than 2500 Greek adults, ages 18 to 89 years, provided the researchers extensive information about their health, diet, and lifestyle each year from 2001 to 2012. The team had access to medical records, and participants completed extensive surveys about their habits at the start of the study, at the 5-year mark, and at 10 years. Dietary patterns for participants were scored on a scale of 1 to 55, based on self-reported intake of 11 food groups.

Those scoring in top third for adherence to the Mediterranean diet were 47% less likely to develop heart disease during the follow-up period, compared with those in the bottom third. Researchers were able to quantify that each 1-point increase in the diet score was associated with a 3% drop in heart disease risk. This difference was independent of other factors such as age, gender, body mass index, smoking status, and family history of heart disease.

"Because the Mediterranean diet is based on food groups that are quite common or easy to find, people around the world could easily adopt this dietary pattern and help protect themselves against heart disease at very little cost," said Ekavi Georgousopoulo, a PhD candidate at Harokopio University in Athens, who conducted the study with Demosthenes B. Panagiotakos, PhD, a professor at the university. **EBDM**

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Prevention of Type 2 Diabetes Requires BOTH Intensive Lifestyle Interventions and Population-Wide Approaches
(CONTINUED FROM COVER)

ANN ALBRIGHT, PHD, RD

The National Diabetes Prevention Program is our greatest opportunity to substantively address T2DM prevention at the "individual" level as well as the "family, friends, small groups" level in the Social-Ecological Model.

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have high rates of poverty and crime.[4] The Social-Ecological Model provides a framework for understanding the multiple levels of influence on health behavior.[5] Its concentric circles describe 4 levels; beginning at the core and moving outward, these are labeled: "individual," "family, friends, small groups," "system, group, culture," and "community and policy." Achieving widespread diabetes prevention requires that we effectively address all 4 levels. Individuals must engage in lifestyle practices (eg, selecting healthy foods, participating in physical activity) that result in modest weight loss (5%-7% of body weight). Individual changes alone are not sufficient, however. In order to make and sustain healthy lifestyle practices, individuals must be supported by family, friends, workplaces, healthcare systems, neighborhoods, and policies (local, state, and national) that promote environments where health is supported and not undermined.

Where are we in addressing the 4 levels of the Social-Ecological Model for diabetes prevention? Most of the evidence currently available for diabetes prevention involves individuals at high risk for T2DM. Several randomized controlled trials (RCT) have demonstrated that a structured lifestyle intervention of sufficient duration (on average, 1 year) that helps participants identify and practice strategies to achieve modest weight loss through reduced calorie intake, increased physical activity, and problem solving can significantly reduce development of T2DM.[6-8] Economic analyses of these structured lifestyle interventions have shown that they are cost-effective.[9] As a result of these RCTs, along with numerous subsequent studies conducted under "real-world" conditions and economic analyses, CDC has established the National Diabetes Prevention Program (National DPP).[10] The National DPP provides a framework to organize lifestyle prevention programs in communities across the United States and implement this proven intervention on a large scale (www.cdc.gov/diabetes/prevention). The 4 components of the National DPP are:

1. Training the workforce (both health professionals and lay people) to implement the program effectively;
2. Establishing a recognition (certification) program by CDC that sets national standards for program delivery and assures quality for participants, healthcare professionals, and payers;
3. Developing a nationwide network of diverse organizations that deliver the lifestyle intervention both in person and through virtual technology, links communities and healthcare organizations, and is part of the healthcare reimbursement system;
4. Engaging in efforts that encourage program participation by those at high risk and referrals from healthcare professionals.

The foundation of the National DPP is a results-driven partnership that includes community-based organizations (including faith-based), health insurers, employers, healthcare systems, academia, and government agencies. For example, the American Medical Association (AMA) has joined CDC in support of the National DPP. As part of this collaboration, CDC and AMA have sounded the alarm with an initiative called Prevent Diabetes STAT: Screen, Test, Act-Today. This rally cry brings together all stakeholders to raise awareness about prediabetes, and to increase screening and referral to diabetes prevention programs that are part of the National DPP. CDC and AMA encourage all sectors to participate in Prevent Diabetes STAT (www.preventdiabetesstat.org).

Thus far, the National DPP has resulted in more than 650 organizations recognized by CDC who are delivering lifestyle interventions to thousands of people at risk for T2DM. There are a growing number of insurance companies and employers who include this cost-effective program as a covered benefit. The National DPP is our greatest opportunity to substantively address T2DM prevention at the "individual" level as well as the "family, friends, small groups" level in the Social-Ecological Model. The National DPP also contributes to addressing the "system, group, culture" level when it is delivered at work sites and community gathering places and becomes a covered benefit in the healthcare reimbursement system.

In order to support the "individual" and "family, friends, small group" levels, fully address the "system, group, culture" level, and tackle the "community and policy" level, a concurrent "populationwide" approach that involves general health promotion, obesity prevention, and policies to improve the behaviors and environment of the population as a whole is needed. Macro-level environmental approaches to reducing population levels of obesity have generated strong evidence that price subsidies for healthier foods influence food purchases, but not necessarily total caloric consumption or body weight.[11] In both cafeteria and vending machine settings, a 50% reduction in prices of fruit, salad, and other low-fat foods led to as much as a 3-fold increase in consumption of these healthy choices. Other proposed targets are strategies to reduce portion sizes and sweetened beverages.[11] Based on observational and experimental studies, the availability and accessibility (including positioning and marketing) of healthy and less healthy foods has an impact on nutritional choices.[12] Community design and work site policies that promote physical activity have been identified as promising targets to increase levels of physical activity in the population.[13]

Research shows that in both cafeteria and vending machine settings, a 50% reduction in prices of fruit, salad, and other low-fat foods led to as much as a 3-fold increase in consumption of these healthy choices.

WHAT MORE NEEDS TO BE DONE?

We have not yet maximized implementation of the National DPP. The program needs to be available to more people in more places. Accomplishing this expansion will require additional payers to provide the program as a covered benefit. In August 2014, the US Preventive Services Task Force recommended offering or referring adults who are overweight or obese and have additional cardiovascular disease (CVD) risk factors (including diabetes and prediabetes) to intensive behavioral counseling interventions to promote a healthful diet and physical activity for CVD prevention.[14] This approach received a B recommendation, which means that health plans must provide coverage for this intervention. The National DPP lifestyle intervention meets this requirement. We must also increase program participation by those at high risk for T2DM. Accomplishing this requires increased screening and testing to identify those with prediabetes and referring them to programs that are a part of the National DPP. Additionally, there is a need for more research and evaluation of strategies to attract people to these programs and enhance retention.

While there are a variety of proposed targets for reducing population-wide risk—some of them mentioned above—these have seen limited implementation. Some of this limited implementation is due to the belief that these changes will limit freedom of choice and place undue constraints on individuals and organizations. One way to address this concern is to conduct "natural experiments" which examine population-target policies in their "nat-

Focusing on Prediabetes Is the Key to Reversing the Rise in Diabetes

JONATHAN LEVER

Recent statistics from the CDC show that 86 million people in the United States have prediabetes, up from 79 million in 2010.1 Without weight loss and moderate physical activity, 15% to 30% of people with prediabetes will develop type 2 diabetes mellitus (T2DM) within 5 years.[1,2] These statistics are alarming, and the impact on the cost of healthcare and the overall well-being of our communities makes slowing the rise of new T2DM cases more important than ever before.

We can greatly reduce the incidence of T2DM by focusing on prevention through diagnosing and treating those with prediabetes, the condition in which individuals have blood glucose levels that are higher than normal, but not high enough to be classified as diabetes.

An estimated 1 in 3 adults in the United States has prediabetes, yet just 11% of those individuals are aware of this diagnosis. People with diabetes are at a high risk of developing not only T2DM, but also other chronic conditions such as heart disease and stroke.[3] While some people see a prediabetes diagnosis as a positive development—an indication that one is "safe"—in reality, having prediabetes is a final wake-up call for individuals to improve their health. By making simple lifestyle changes, such as eating better and increasing physical activity, people with prediabetes can delay or prevent the onset of T2DM.

Making lifestyle changes sounds easy, but the reality is many Americans either don't know they are at risk or are challenged in terms of how to make the necessary behavior changes to stave off disease.

The first step is educating the millions of Americans who have prediabetes that they are at risk. Patients can take the CDC's online risk assessment,[4] and physicians can proactively bring up the possibility of prediabetes with patients who have known risk factors. To make this happen, organizations like the American Medical Association are working to educate doctors on the importance of diagnosing prediabetes and recommending treatment solutions.[5]

Once diagnosed, the second step is to help patients modify behaviors to improve health. This is where programs that are part of the CDC's National Diabetes Prevention Program can help. For example, at the Y, more than 31,000 participants in YMCA's Diabetes Prevention Program have lost an average of 5.6% of their body weight by working with a trained lifestyle coach.[6] (These programs are available at 173 YMCA associations in 43 states.)

Participants meet in small groups to learn about healthy eating, physical activity, and other lifestyle changes, with the ultimate goal of losing 5% to 7% of body weight and increasing physical activity to 150 minutes per week.

These intervention programs, delivered outside of a healthcare setting, have been shown to reduce the number of new cases of T2DM by 58% in all adults and by 71% for people 60 years or older.[7] By increasing the awareness and treatment of prediabetes, we can improve the health of our country and save billions in healthcare costs. **EBDM**

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Everyone has a stake in turning the tide on diabetes, because they are impacted either directly by the burdens this disease can inflict or indirectly through the burdens it places on society.

ural" environment (once they have been implemented), using experimental and quasi-experimental designs, to understand how these policies affect preventive behaviors and health outcomes.[15] Providing a stronger understanding of the impact on health and identifying the unintended consequences will help pave the way for implementation of more effective policies.

Several aspects of the etiology of T2DM point to the fact that both the structured lifestyle intervention in the National DPP and population-wide approaches that create a culture of health are necessary to make a major impact on the diabetes epidemic. It is through this combined approach that we will be able to address the multiple levels of influence on health behaviors. Everyone has a stake in turning the tide on diabetes, because they are impacted either directly by the burdens this disease can inflict or indirectly through the burdens it places on society.

What are you doing to implement the National DPP, create healthy communities, and prevent diabetes STAT? **EBDM**

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Building Community-Clinical Linkages to Address the Diabetes Epidemic
(CONTINUED FROM COVER)

BRENDA SCHMIDT, MS, MBA

"Ideally, population health technology links clinical, community, and social systems to address the needs of patients and communities. Data sharing between sectors can be complicated and difficult, in part due to safeguards to protect patient privacy."

- a clinical epidemiology perspective
- evidence-based practice
- focus on outcomes
- emphasis on prevention.[1]

They contend that widespread awareness and adoption of these principles will have a profound impact on medical and public health education, practice, and ultimately the public's health.[1]

DIABETES INCIDENCE, IMPACT, AND OPPORTUNITY

The United States is facing a looming diabetes epidemic. Diabetes affects 29 million Americans—nearly 10% of the population—and another 86 million American adults are estimated to have prediabetes, a condition that puts them at high risk for developing type 2 diabetes mellitus (T2DM). Between 15% and 30% of individuals with prediabetes who are overweight will develop T2DM within 5 years. Without prevention, 1 out of every 5 American adults will develop T2DM by 2025, and 1 out of 3 by 2050.[2] T2DM has a disparate impact on racial and ethnic minorities. The risk of developing T2DM is 77% higher among African Americans, 66% higher among Latinos, and 18% higher among Asian Americans compared with Whites. Native Americans are even more disparately affected by diabetes. Nationwide, 16% of Native American adults are diagnosed with the disease, with rates soaring as high as 33% for some Tribal communities in the Southwest.[3]

In addition to a significant human toll, the financial cost of diabetes is staggering. In 2012, the total estimated cost of diabetes in the United States was $245 billion. The growth in the prevalence of T2DM predicts that direct medical costs will soar in the next 2 decades.[4]

Fortunately, T2DM is largely preventable. One of the most important keys to reversing this epidemic is increased access to evidence-based diabetes prevention programs for populations at high risk for developing diabetes. The solution requires a collaborative effort by healthcare, public health, employers, insurers, and community organizations. The National Diabetes Prevention Program (National DPP) is the "gold standard" for diabetes prevention, with proven outcomes in multiple randomized controlled trials. The National DPP is a year-long community-based program delivered in a group-based setting in the community—or more recently, delivered virtually—supported by a trained lifestyle coach. The program helps people modify their eating and physical activity habits and learn how to sustain lifestyle changes over time with a modest 5% to 7% weight loss goal. The National DPP has been shown to reduce the risk of developing T2DM by 58% for adults age 25 years and older with prediabetes, and by 71% for adults older than 60 years [5,6]

THE NEED FOR COMMUNITY-CLINICAL LINKAGES

Scaling the National DPP in communities across the nation is a critical step in combating the diabetes epidemic. The National DPP does not need to be tethered to a primary care setting. Numerous studies have cited the efficacy of the program as delivered by trained lay health educators in a variety of community locations.[7]

Effective promotion of population health, including the prevention and control of diabetes, can only happen through true community collaboration that includes public health, social services, environmental support, and integrated community providers. Indeed, true improvements in population health require a broad-based approach that addresses a full range of social determinants of health—from nutrition to employment to housing. One of the values of community-based delivery is the opportunity to refer participants to additional programs and services. When coordinating care with community-based providers of the National DPP, primary care providers are introduced to the social conditions and community experience of their patients, such as poor housing. Those insights often lead providers to a new awareness of the need to address social conditions in order to improve health. Over the long term, changing expectations and new approaches to community-based population health will foster strong partnerships with community-based organizations in order to address the social, emotional, and behavioral determinants of health as an adjunct to primary care.

BARRIERS TO EFFECTIVE COMMUNITY-CLINICAL LINKAGES

Currently, 625 organizations have been granted pending or full recognition status as National DPP providers by the Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/diabetes/prevention/recognition).[8] Considering the 86 million people at high risk for developing T2DM, the need for a scalable, integrated DPP network is clear. However, disparate community-based and virtual DPP providers are not supported through a coordinated approach to patient identification, referrals, program delivery, and payment.

Physicians and other healthcare providers are encouraged to screen and refer high-risk patients to National DPP providers in their communities, or more recently, to virtual diabetes prevention programs. One challenge they face is the lack of a centralized searchable database or services directory for easily referring and enrolling patients into a "best-fit" program based on language, location, convenient class day, and convenient time. At present, healthcare providers can supply their eligible patients with a list of organizations offering the National DPP, relying on the patient to follow up directly with a provider organization. Unfortunately, these lists quickly become outdated due to the welcome proliferation of organizations offering the National DPP, including virtual DPP programs. Viridian has found that this this type of "opt-in" approach tends to result in significantly lower enrollment and engagement.

Community-based organizations delivering the National DPP, including the Black Women's Health Imperative, the American Association for Diabetes Educators (AADE), the YMCA of the USA, and many faith-based organizations, are well suited to meet the diverse cultural needs of their local community members at high risk of developing T2DM. These community-based organizations are typically not established partners to healthcare providers and insurers. They usually lack the operational infrastructure and systems necessary to manage and store large sets of data, or meet privacy and security standards required by the Health Insurance Portability and Accountability Act and the Health Information Technology for Economic and Clinical Health Act. They may not be ready to comply with health plan delegate oversight requirements, manage physician referrals, and submit claims to be reimbursed for their services. These organizations often do not have the technology to securely manage data from a variety of data sources and referral channels to identify individuals with prediabetes and manage the robust reporting requirements for employers, physicians, and insurers.

Insurers are beginning to adopt the National DPP as a covered benefit for their members. While this is an encouraging development, systems must be in place to support the delivery of the National DPP across large populations. Most National DPP providers do not have the infrastructure in place to submit medical claims for their services. To ensure regional, statewide, and/or national capacity to cover plan members, health plans would need to contract independently with each community-based or virtual National DPP provider. Because so many community-based organizations find it difficult to comply with health plan delegate oversight requirements, the network of National DPP providers serving health plans is small and composed mostly of health-system–based programs. In 2010, UnitedHealthcare established the Diabetes Prevention and Control Alliance to address these issues and establish a mechanism to facilitate community-clinical linkages to replicate the Y-DPP program through a national network of YMCAs.[9]

VIRIDIAN HEALTH MANAGEMENT: CREATING COMMUNITY-CLINICAL LINKAGES

While physicians, insurers, employers, and community-based organizationsthere face many challenges to creating effective community-clinical linkages, successful models of integration are emerging. In November 2013, Trust for America's Health convened national experts and local innovators to define practical steps to build a system that improves population health and reduces health disparities. The result was a summary report titled "Twin Pillars of Transformation: Delivery System Redesign and Paying for Prevention" (Trust for America's Health, 2013). The report summarized successful emerging best practices and specifically called out the need for an "integrator" that coordinated alignment across clinical systems and community prevention.[10]

Viridian Health Management is a national corporation devoted to improving population health. Due to Viridian's historic focus on the integration of public health, employee wellness, and clinical care, Viridian recognized the need for an "integrator" role to support the unification and alignment across a variety of National DPP stakeholders—to support program reimbursement, referrals, and program delivery. Information technology capacity is a core function of the integrator. Ideally, population health technology links clinical, community, and social systems to address the needs of patients and communities. Data sharing between sectors, however, can be complicated and difficult, in part due to safeguards to protect patient pri-

vacy. While privacy regulations can be a barrier, they are not an insurmountable challenge. To achieve this, Viridian developed a module of its Maestro population health management technology. Maestro specifically supports the National DPP and other evidence-based chronic disease prevention and control programs that are delivered by community-based organizations and integrated across systems. Viridian provides the Maestro SaaS-based platform at no charge to Viridian's national network of community-based organizations to facilitate National DPP class management, data collection, and reimbursement by payers.

Through direct contracting with health plans, Viridian serves as a managed services organization to provide the operational infrastructure and technology needed to broadly scale the National DPP, and assumes the responsibilities for patient qualification and enrollment, data privacy and security, reporting, delegate oversight, physician referrals, and compliance. Viridian forms partnerships with organizations recognized by the CDC as National DPP providers, and provides administrative support to identify eligible patients; reaches out to and engages participants; provides a centralized database of providers, classes, and virtual programs; and enrolls participants into a National DPP program that best meets their needs. Viridian's network includes a wide variety of organizations that deliver the National DPP and are paid by Viridian when they achieve program milestone goals, including attendance and weight loss. Program reimbursement provides a sustainable revenue model for community-based providers that frequently rely on grant funding to support the costs of delivering the program.

Collaboration with community-based organizations that have widespread reach and are highly trusted and known to members of a community are key to scaling the National DPP. No single organization has the capacity to provide the National DPP with more than a small share of the 86 million individuals who would benefit from the program. Community-clinical linkages as an extension of primary care provide a model to address population health and chronic disease prevention and control as a best-practice model for population health. **EBDM**

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Real-World Evidence Mounts for Rivaroxaban

(CONTINUED FROM COVER)

attack, heart failure, myocardial infarction, diabetes or moderate renal dysfunction," wrote the authors of a recent article in *Expert Review of Cardiovascular Therapy*. "Moreover, recent data have confirmed the efficacy and safety of rivaroxaban in real-life practice."[5]

Such findings have helped NOACs like rivaroxaban take market share from warfarin, a vitamin K antagonist that has long been a mainstay of AF treatment because it is a very potent antithrombotic agent.

The efficacy of warfarin does vary, not only among different types of AF patients with different comorbidities, but also among different individual patients who appear medically relevant. That said, a meta-analysis of studies with more than 28,000 patients calculated that the drug reduced stroke risk by an average of 64%.[6]

Unfortunately, warfarin is a famously difficult medicine to use. Its narrow therapeutic window offers patients little protection against stroke at international normalized ratios (INRs) below 2.0, and produces unacceptable bleeding risks at INRs above 3.0. Worse, the dose needed to keep patients inside this narrow therapeutic window varies from patient to patient, and the dose needed to keep any given patient within this range varies from time to time. The only way to keep patients in the therapeutic zone is to perform repeated blood tests throughout the patient's life and make adjustments as needed.

Patients must submit not only to this testing regime but also to the dietary and medical restrictions needed to prevent interactions between warfarin and various other drugs and foods. Indeed, there is some evidence that warfarin interacts with α-glucosidase inhibitors that are sometimes used to treat diabetes.[7]

These drawbacks, along with the fear of intracranial hemorrhages and other major bleeds, have always led many patients to refuse warfarin treatment and many others to abandon the drug after using it for a short period. Estimates vary, but some suggest that half of all patients who would benefit from warfarin never try it[8] and that half of those who try it discontinue treatment within 5 years.[9]

Such decisions often prove fatal. Even in the absence of significant comorbidities, AF is associated with a 5-fold increase in the risk of ischemic stroke. Certain common comorbidities increase the risk further still: prior stroke/transient ischemic attack (relative risk [RR], 2.5; 95% CI, 1.8-3.5), hypertension (RR, 2.0; 95% CI, 1.6-2.5), diabetes mellitus (RR, 1.7; 95% CI, 1.4-2.0), and increasing age (RR, 1.5 per decade; 95% CI, 1.3-1.7).[10]

These numbers illustrate the lifesaving potential of any drug that could match (or exceed) the efficacy and safety of warfarin—without all the difficulties that discourage patient adherence. The phase 3 trial that led the FDA to approve rivaroxaban in late 2011 indicated that the newcomer had the potential to be just such a drug.

Real-world findings have helped novel oral anticoagulants take market share from warfarin, a vitamin K antagonist that has long been a mainstay of atrial fibrillation treatment.

Researchers who randomized 14,264 AF patients between the 2 drugs and followed them for an average of 707 days found that the rates of stroke or systemic embolism in the intention to treat analysis were 2.1% per year for rivaroxaban and 2.4% per year for warfarin (hazard ratio [HR], 0.88; 95% CI, 0.74-1.03; P <.001 for non-inferiority, P = .12 for superiority).[11]

Rivaroxaban also boasted several other obvious advantages over the older medication. It came in just 2 doses—15 mg for people with impaired kidney function and 20 mg for everyone else—and thus required no monitoring or dose adjustments. It placed no restrictions on what patients could eat or what other medications they could use. It was even associated with a far lower risk of intracranial hemorrhage (HR, 0.67; 95% CI, 0.47-0.93; P = .02).[11]

Yet despite all those advantages, the trial indicated that patients were just as likely to stop taking rivaroxaban as they were to stop taking warfarin. Discontinuation rates were 23.7% for rivaroxaban and 22.2% for warfarin.[11]

Now, a large study of real-world rivaroxaban use concludes that the discontinuation rates reported by the phase 3 trial say more about trial design than actual patient behavior.

That study—which took data from an ongoing, prospective, noninterventional registry that is following more than 1204 rivaroxaban users in Germany—found that about 15% of patients discontinued rivaroxaban at some point in the first year of treatment and only about 3% of patients discontinued it at any subsequent point.[2] This compares very favorably to studies of warfarin among real-world pa-

PETER R. KOWEY, MD

Cost-effectiveness studies with novel oral anticoagulants have caused payers to rethink their resistance to using this class for first-line treatment, Kowey told *EBDM*.

FRANKLIN MADDUX, MD, FACP

"Warfarin has a longer history of use and we know much about its risks and characteristics of use, but it's up to individual physicians to know their individual patients and the options for use of traditional or novel agents."

tients (as opposed to those in clinical trials), which have found first-year discontinuation rates as high as 30% and 3-year discontinuation rates of 50%.[9,11]

Another recent study—a retrospective matched-cohort study of American patients—found that treatment persistence at 6 months was 81.5% for rivaroxaban and just 68.3% for warfarin.[14] "Even more importantly, the persistence rates for rivaroxaban reported by Laliberté et al, and confirmed in our study, are substantially higher than those reported for [vitamin K antagonists] in daily care settings," wrote the authors of the German study in *Europace*.

Dramatically higher persistent rates could translate into substantially fewer strokes overall, and the persistence figures were not significantly different for most of the subgroups the German researchers broke out from the total cohort. Patients with renal impairments, prior strokes, arterial hypertension, and prior discontinuation of warfarin were about as likely as the general population to stick with rivaroxaban.

The only subgroup that was significantly less likely than average to discontinue treatment consisted of patients with unusually low body mass index (HR, 0.74; 95% CI, 0.55-0.99; *P* = .04).

The only 2 subgroups that were significantly more likely than average to discontinue treatment consisted of patients with diabetes (HR, 1.35; 95% CI, 1.03-1.77; *P* = .03) and patients with transient ischemic attack, stroke, or systemic embolism (HR, 1.41; 95% CI, 1.08-1.85; *P* = .01). The most common reasons for rivaroxaban discontinuation among the cohort as a whole were bleeding (30%), other side effects (24.2%), and resumption of sinus rhythm (9.9%).

The paper's lead author, Jan Beyer-Westendorf, MD, declined to specify why patients with diabetes were more likely than others to stop taking rivaroxaban, but future papers from his study group should help physicians decide whether to try such patients on rivaroxaban or some alternative. "We are planning to look at several subgroups including diabetic patients," he wrote in an e-mail. "However, we are still in the follow-up phase [of the Dresden NOAC study] and perform only a few interim analyses. Therefore, we do not have answers at present."

The years since rivaroxaban's initial approval have also brought a steady stream of information about its safety and efficacy in AF patients with various comorbidities. Most of that information has been mined from the drug's phase 3 trial data, and most of it has been encouraging.

To start with the 2 populations that were unusually likely to discontinue rivaroxaban in the German study—those with diabetes and those with a history of stroke—analyses suggested that both groups might fare marginally better with rivaroxaban than warfarin. The risk of stroke or systemic embolism was very nearly (but not quite) significantly lower among diabetic AF patients who took rivaroxaban rather than warfarin (HR, 0.74; 95% CI, 0.54-1.01; *P* = .055) and overall bleeding risks were nearly identical.[13]

In patients with prior strokes, rivaroxaban performed slightly better than warfarin but, again, it was close enough that it may have been by chance (HR, 0.94; 95% CI, 0.77-1.16). The same was true when researchers calculated the risk of intracranial hemorrhage (HR, 0.74; 95% CI, 0.47-1.15) and fatal bleeding (HR, 0.54; 95% CI, 0.29-1.00).[15]

Results were very similar among AF patients who had suffered heart failure,[16] ischemic cardiovascular events,[17] and peripheral artery disease,[18] as well as patients over and under 75 years of age.[19]

Analysis of the effects of rivaroxaban in patients who were experienced with and naïve to vitamin K antagonists again showed comparable benefits, but it did suggest something that the authors of the clinical review thought clinicians should note: the possibility that patients are particularly susceptible to major bleeds when they are making the transition from one drug to the other.[1]

Subgroup analysis of AF patients with mild renal failure (creatinine clearance between 30 and 49 mL/min) again found that such patients (who received 15 mg of rivaroxaban rather than 20 mg) suffered fewer strokes, embolisms, and bleeds than those who received warfarin but not consistently enough to demonstrate superiority.[20] This last finding should be of particular interest to physicians who treat patients with both AF and T2DM, for the latter disease ranks among the biggest causes of renal impairment.

AF patients with advanced kidney disease or on dialysis were not eligible for the trial, but subsequent retrospective analysis of real-world patient outcomes suggests that physicians should, at the very least, think twice before prescribing the medication for them.

Such prescriptions of rivaroxaban and dabigatran, for patients with advanced renal disease, currently do not have an FDA indication, partially because the drug is metabolized by the kidneys; however, a recent study in *Circulation*[21] found that doctors currently prescribe either rivaroxaban or dabigatran to 5.9% of all AF patients on hemodialysis who require anticoagulation. When the authors of the study compared outcomes of hemodialysis patients on rivaroxaban with those on warfarin, they found that rivaroxaban was associated with an increased risk of hospitalization or death from bleeding compared with warfarin (RR, 1.38; 95% CI, 1.03-1.83; *P* = .04).

> *"In certain patients with rare clinical conditions that make them intolerant to warfarin, rivaroxaban might be a reasonable choice."*
>
> —FRANKLIN MADDUX, MD, FACP

"The challenge with all anticoagulants is to balance the reduction in stroke risk with the increase in bleeding risk. The equation is different in patients with renal failure, however, because they start off with a significantly elevated risk of significant bleeding," said coauthor Franklin Maddux, MD, FACP, chief medical officer at Fresenius Medical Care North America, in an interview.

"In general, warfarin has a longer history of use and we know much about its risks and characteristics of use, but it's up to individual physicians to know their individual patients and the options for use of traditional or novel agents. In certain patients with rare clinical conditions that make them intolerant to warfarin, rivaroxaban might be a reasonable choice."

Although the total number of AF patients who need hemodialysis is small (perhaps 50,000 patients in all), physicians should probably exercise substantial caution when prescribing rivaroxaban or dabigatran to patients with advanced kidney disease. "Because the medication is cleared by the kidneys, a progressive loss of function over time could lead to increasing concentrations of the medication in the blood and increasing risk of serious bleeds," said coauthor Kevin E. Chan, MD, a nephrologist at Massachusetts General Hospital, in an interview. "When physicians prescribe rivaroxaban to patients who are at risk of progressive failure, they should routinely monitor kidney function, and when they see signs of deterioration, they should check concentrations of medication in the blood. Subsequent research may show this to be unnecessary, but we don't know yet."

Follow-up studies have also investigated aspects of rivaroxaban that are not purely medical.

For example, a paper published in the *American Journal of Cardiology*[22] used phase 3 trial data to determine the cost-effectiveness of the drug, which retails for about $380 a month, compared with warfarin, at roughly $15 a month.[23] The study found that patients treated with rivaroxaban added an average of 10.03 quality-adjusted life years (QALYs) at a lifetime treatment cost of $94,456, while those receiving warfarin added an average of 9.81 QALYs and incurred costs of $88,544. The incremental cost-effectiveness ratio for rivaroxaban was $27,498 per QALY.

"Time horizon, Monte Carlo simulation demonstrated rivaroxaban was cost-effective in 80% and 91% of 10,000 iterations at willingness-to-pay thresholds of $50,000 and $100,000 per QALY, respectively," the study authors wrote, referencing the business model used to predict risk. "In conclusion, this Markov model suggests that rivaroxaban therapy may be a cost-effective alternative to adjusted-dose warfarin for stroke prevention in AF."

Peter R. Kowey, MD, a researcher who also treats patients with AF, said in an interview that payers, who refused to cover rivaroxaban and other NOACs as first-line treatment when they hit the market, began rethinking their policy after the cost-effectiveness studies were published (and they reached pricing deals with drug makers).

The generally positive findings from

Rivaroxaban Postmarketing Study Continues to Find Fatal Bleeds Are Rare

MARY K. CAFFREY

Researchers responsible for the postmarketing studies of rivaroxaban, a novel oral anticoagulant used to prevent stroke and for other indications, updated their data at the 64th Annual Scientific Sessions of the American College of Cardiology (ACC),[1] but reached the same conclusions as before:

- Risks of major bleeding are low
- Deaths from major bleeding are rare
- Results, now based on a review of 31,833 patient records, are consistent with the registration trials that led to the drug's approval.[1]

The study team, led by Sally Tamayo, MD, head of cardiology at the Naval Medical Center of Portsmouth, Virginia, first published its conclusions based on 15 months' worth of results for 27,467 patients in *Clinical Cardiology* in February 2015.[2] The update, with 18 months' worth of data on more patients, was presented March 15, 2015, at the ACC meeting in San Diego.

Rivaroxaban, marketed as Xarelto, is approved for 6 indications. FDA approved the first 2 in 2011, including the drug's use to prevent stroke for those with nonvalvular atrial fibrillation (NVAF).[3] As part of an FDA postmarketing requirement, a 5-year observational study was designed to evaluate major bleeding risks among a much larger group of patients taking the drug for that purpose.

Using a validated database method (Cunningham algorithm), 9.7 million electronic medical records from the Department of Defense were examined, yielding 31,833 patients from January 2013 through June 2014. Major bleeding–related hospitalizations among those with NVAF were examined. Major bleeding events included gastrointestinal bleeding, hemorrhagic strokes and other intracranial bleeds, and genitourinary bleeding.

Of the rivaroxaban patient population identified, 622 experienced at least 1 major bleeding event, for an incidence rate of 2.85 per 100 person-years [95% CI, 2.63-3.08].

Those experiencing major bleeding events were older, with a mean age of 78.7 years, compared with a mean age of 75.8 years for those who did not experience such an event. Among those experiencing a major bleeding event, 50.5% were men; in the other group, 55.6% were men. Comorbidities were more common among those experiencing major bleeding events, especially hypertension (94.1%) and coronary artery disease (72.1%). Those without major bleeding had lower rates of hypertension (62.5%) and coronary artery disease (34.4%).

The most common major bleeding site was gastrointestinal (88.3%), followed by intracranial (7.7%). Care included transfusions (37.3%), and most major bleeding patients were sent home (73.8%). During the study period, 20 patients with major bleeding (average age 82.1 years) died during hospitalization, at a fatality rate of 0.09 per 100 person-years [95% CI, 0.04-0.150.] Fatalities were higher among those with intracranial bleeds (29.2%; 14 of 48 cases) compared with gastrointestinal bleeds (1.1%; 6 of 549 cases). **EBDM**

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most follow-up research into the entire class of medications has increased acceptance and answered many questions that clinical trials never did.

There is, however, a major question that research is unlikely to answer at any point in the future: how the NOACs compare against each other in terms of efficacy and safety.

"Assuming the differences among them are not so large that they could be demonstrated conclusively via retroactive analysis of patient records—and there's no reason to think the difference is that large—the only thing that would answer that question is a massive randomized trial that pitted them against each other," said Kowey, who is the director of the Center for Clinical Cardiology at the Lankenau Institute for Medical Research.

"That, of course, would be very expensive and there is no incentive whatsoever for any company to foot the bill, so we'll probably never know for sure which anticoagulant to prescribe for which patient. Still, we can say, with a fair amount of confidence at this point, that this class of medication has substantial advantages over warfarin, and that's a step forward." **EBDM**

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