Health Monitor®

Clinician Update

Type 2 Diabetes Management

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Content reviewed by:

AACE®

OVERCOMING CLINICAL INERTIA: **The key to better outcomes**

Intensifying therapy to reach targets sooner can help stave off complications and improve quality of life. Here, experts offer strategies to proactively manage diabetes.

Clinical inertia—the failure to initiate or intensify treatment despite evidence of a need for a change in therapy—contributes to inadequate chronic disease care in patients with diabetes. Even more concerning is evidence that clinical inertia related to the management of diabetes, hypertension and lipid disorders may result in up to 80% of heart attacks and strokes.[1]

Jay Shubrook, DO, Professor in the Primary Care Department at Touro University in California and coauthor of a recent review on clinical inertia in *Diabetology*, says that despite the evolution in treatment options and improved understanding of pathophysiology, the treatment of type 2 diabetes remains unsatisfactory.[2] The study concluded that "intensive lifestyle modification, pharmacologic approaches and metabolic surgeries are each viable options for improving outcomes when implemented early in the disease course." When put into practice promptly, these treatment options can help patients reach their target goals and achieve optimal control. It's important to note, however, that healthcare providers must work closely with their patients and apply strategies for overcoming inertia to achieve treatment goals.

"Many people think diabetes progresses inevitably to complications," says Dr. Shubrook. "But if patients are willing to get screened, find the condition early and 'go big' in terms of treatment, their diabetes can be well controlled, significantly reducing the risk of complications. He stresses that treating diabetes is most effective in the first 2 years of the disease.

Continued on p. 4 ►

Illustration by Keith Negley

When treating diabetes, targeting blood pressure and LDL cholesterol is as crucial as controlling blood glucose. Evidence-based therapies to manage cardiometabolic risk factors include:

- Two classes of antihyperglycemics: GLP-1 receptor agonists (GLP-1 RAs) and SGLT2 inhibitors, which help reduce the risk of cardiovascular disease independent of their ability to lower glucose. SGLT2 inhibitors are also indicated for treating chronic kidney disease and heart failure
- ACE inhibitors and angiotensin receptor blockers (ARBs) for hypertension
- Statins to reduce LDL cholesterol

More options for tailored treatment

Betul Hatipoglu, MD, Director of the Diabetes and Metabolic Care Center at UH Cleveland Medical Center, recommends individualization of medication and treatment for patients. Prescribing metformin, although still a mainstay of treatment, is usually not enough by itself to maintain long-term control.[3] "Metformin has been around for a long time, and it's a safe medication," Dr. Hatipoglu says. "But we now have more tools in our toolbox, and we can do more specialized and individualized therapy for our patients."

GLP-1 RAs and SGLT2 inhibitors target not only blood sugar but also diabetes-related complications. Medications like these have allowed the treatment of type 2 diabetes to shift from a focus solely on lowering A1C to prioritizing agents with proven cardiovascular and renal benefits. According to a recent real-world study, combination therapy with SGLT2 inhibitors and GLP-1 RAs resulted in a 34% decreased risk of myocardial infarction, ischemic stroke and cardiovascular mortality.[4]

Statins and ACE inhibitors also allow for more specialized and individualized therapy. The AACE diabetes guidelines emphasize that any patient with diabetes who has cardiovascular disease, or is at high risk of it, should be receiving treatment to lower their LDL cholesterol and blood pressure.[5] "The best thing we can do for our patients is remind them that front-loading their regimen by getting control of glucose, blood pressure and lipids immediately upon diagnosis will have lasting effects," Dr. Shubrook advises. "The earlier we control this disease by considering all options, the easier it is to tame it, and the greater the potential for subtracting treatments down the road."

Dr. Shubrook also notes that in addition to antidiabetes medication, bariatric surgery may be an option for certain patients. In one study of insulin-treated patients with type 2 diabetes, gastric bypass surgery resulted in an improvement in A1C from 11.8% to 7.9%.[6] Of course, any surgery comes with risks, and patients with blood clots, liver disease and kidney stones may experience a worsening of these conditions post-surgery.

Strategies for proactive management.

To help your patients achieve treatment targets and, ultimately, optimal outcomes, experts recommend the following:

1. Follow up often.

Regular monitoring of treatment goals and providing feedback to patients can help identify situations where intervention is needed. This can be achieved through regular follow-ups and by answering questions. In addition, Dr. Shubrook suggests that clinicians also try to put themselves in their patients' shoes. "If you are teaching me something new, like learning how to drive, you can't just give me a manual and say come back in 3 months," he says. "I wouldn't know where to begin." He recommends a minimum of 4 follow-up visits per year.

2. Incorporate team-based care.

"The touchpoints we have for our patients don't always have to be physicians," notes Dr. Shubrook. "We can utilize healthcare educators, community health workers, nutritionists and mental health professionals." Each team member can contribute their expertise and perspectives to help patients navigate their disease and ensure comprehensive and timely treatment changes between office visits.

3. Empower patients to be an equal partner in care.

In many cases, patients can be overwhelmed by the amount of treatment being recommended. "You have to be careful about how you approach your patients and how you recommend treatments to them," Dr. Hatipoglu advises. "As their clinician, you must help them understand the importance of getting treatment and managing their diabetes." Involving patients in shared decision-making and setting realistic goals together can empower patients to take control and be proactive in diabetes self-management. Also, when several recommendations are presented at once, it can be overwhelming. If patients implement one option at a time and build on it promptly, it can be more manageable.

Illustration by Keith Negley

4. Address adherence issues up front.

Many patients have no idea that they even have diabetes because it's a "silent" condition. "Patients often feel okay before they come to see me, and treatment may make them feel worse because they are 'detoxing,'" Dr. Hatipoglu says. "When starting diabetes medications and working to lower blood sugar, patients may experience side effects such as dizziness, sweating and confusion. This can cause patients to become nonadherent to their treat-

"WE NOW HAVE MORE TOOLS IN OUR TOOLBOX, AND WE CAN DO MORE SPECIALIZED THERAPY."
—BETUL HATIPOGLU, MD

ment regimen. It's important to help them understand that they'll ultimately feel better as their body adjusts." In addition, Dr. Shubrook says clinicians must investigate the reason for nonadherence. "Adherence for many patients boils down to engagement," he says. "If a patient is struggling to keep up with their medication regimen, you should know why. Is it because they can't afford the medication? Is it because of intolerable side effects?"

5. Help them overcome financial barriers.

"We must remember to meet patients where they are, and that some treatment is better than no treatment if they can't afford what I recommend," Dr. Shubrook says. Fortunately, insurance coverage for newer diabetes medications, statins and ACE inhibitors is becoming more commonplace.[7] It's important to become familiar with available resources for your patients, such as pharmaceutical patient assistance programs and co-pay cards as well as other options, such as *insulinhelp.org*. A pharmacist or social worker can also help patients find assistance programs they may be eligible for.

6. Stress the importance of lifestyle modification.

Lifestyle changes are key in the management of type 2 diabetes, particularly for patients with overweight/obesity who start a weight-loss plan. However, set realistic expectations for your patients. "People often think that 3 months of lifestyle modifications, which is a lot of work for most people, is going to change things immediately and when it doesn't, they end up believing it doesn't work." Encouraging your patients to continue with healthy habits, such as controlling portion sizes and being physically active for at least 30 minutes a day, can result in a loss of about 10 to 20 lbs. over time.[8]

For patients who smoke, quitting will vastly improve their health. In patients who have diabetes, smoking increases the risk of nerve damage, kidney disease and premature death from cardiovascular disease.[8] Advocate for your patients and give them resources to help them quit, such as 1-800-QUIT-NOW or *smokefree.gov*.

Ultimately, a better understanding of clinical inertia and specific interventions to address it can help reduce diabetes-related morbidity and mortality. "Decide who is going to be on the diabetes team," Dr. Shubrook says. "Whether it's nutritionists, PCPs or diabetes educators, utilize everyone as a resource and take the time to understand your patient and what works for them." ●

—by Rikki Eccles

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Keeping glucose levels within a SAFE RANGE

Increasingly, researchers assert that frequent swings in blood glucose warrant closer attention. Here's why—and how to help patients avoid it.

Patients with type 2 diabetes who experience high levels of glycemic variability (GV)—that is, frequent dips and spikes in blood glucose levels throughout the day—may be at increased risk for complications, according to an expanding body of scientific evidence. While more research is needed, there's no dispute that chronically high or low blood glucose, as well as dramatic swings, can have devastating effects.[1,2]

How fluctuations may contribute to complications

Over the years, as patients began doing more frequent self-monitoring of blood glucose, clinicians began to notice that some patients had wildly fluctuating levels. Lab research soon suggested that high levels of GV may be a concern. "In cell cultures, you do more bad things to the cell when you have variable glucose levels than when you keep the glucose levels stable—even at high blood sugar levels," says endocrinologist Irl Hirsch, MD, Professor of Medicine at the University of Washington School of Medicine. Research has shown that diabetes patients with the highest GV have more oxidative stress—that is, an imbalance between production of tissue-destroying free radicals and protective antioxidants that has been implicated as a cause of diabetes complications. This may help explain why patients with high GV have an increased risk of nephropathy, peripheral neuropathy, retinopathy and cardiovascular disease—even if their A1C is at goal.[1-3]

However, not all studies support the theory that GV is an independent risk factor for com- plications (e.g., this was not confirmed in the DCCT trial for patients with type 1 diabetes).[4] "We don't have randomized trials to conclude whether glycemic variability leads to complications," says Dr. Hirsch. "I am the first to say that. But it makes sense that it has some impact." One thing that's known for sure: Nearly 500,000 patients with diabetes visit the emergency department each year for hyperglycemic crisis or hypoglycemia, according to the CDC.[5]

The dangers of hypoglycemia

While debate continues over whether GV is a risk factor for complications, the perils of persistently low blood glucose are evident. In early stages, hypoglycemia causes perspiration, hunger, jitters and anxiety. If not treated by the patient (e.g., by consuming 15 to 20 grams of simple carbohydrates), it can become severe and result in confusion and cognitive impairment. What's more, emerging data suggest that recurrent episodes of hypoglycemia may increase the risk for cardiovascular disease.[1,3]

Frequent bouts of hypoglycemia also promote the dangerous phenomenon known as hypoglycemia unawareness. "For patients who have recurrent exposure to low blood sugar, the threshold for development of the symptoms of hypoglycemia shifts to a lower plasma glucose level. Continued exposure to iatrogenic hypoglycemia in these patients can lead to development of hypoglycemia unawareness, in which the first sign of low blood sugar can be alteration in cognition, seizure or loss of consciousness," says Amir Moheet, MD, Associate Professor of Medicine (endocrinology) at University of Minnesota Medical School.

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Illustration by Keith Negley

Assessing glycemic control: What factors can affect A1C

Hemoglobin A1C, which measures average blood glucose over a 3-month period, has long been the gold standard for gauging whether a patient's blood glucose is well controlled, and for good reason: It has strong predictive value for diabetes-related complications. However, A1C provides limited insight into glucose control *patterns* over a 3-month period. Here are some factors that may affect a patient's A1C results[10]—and necessitate further investigation (e.g., with continuous glucose monitoring) to make sure their blood glucose stays in a safe range:

- **Conditions that affect red blood cell turnover such as:**
  - Hemolytic and other anemias
  - Glucose-6 phosphate dehydrogenase deficiency
  - Drugs that stimulate erythropoesis
  - Recent blood transfusion
  - End-stage renal disease
  - Pregnancy
- **Hemoglobinopathies**
- **Liver disease**
- **Treatment of iron or vitamin B_{12} deficiency**
- **Genetic/racial differences (e.g., different rates of glycation of hemoglobin)**

Diabetes patients who develop hypoglycemia unawareness become unable to recognize the telltale symptoms of dropping blood sugar levels, which may allow hypoglycemia to worsen and become severe and potentially fatal. Dr. Moheet, who studies hypoglycemia unawareness, notes that the exact etiology is not fully understood, but it may occur due to altered sensing of hypoglycemia in the brain and nervous system. While frequent hypoglycemic episodes and hypoglycemia unawareness are concerns for anyone with diabetes, certain patients are most at risk when blood sugar drops too low, including people with safety-sensitive occupations (e.g., commercial truck drivers, pilots, workers who operate hazardous machinery) and older patients, who risk bone fractures from increased risk of falls.[6]

Strategies for detecting highs and lows

While A1C is the preferred measurement for assessing glucose control in diabetes, it provides information about average blood glucose over only 3 months, says Dr. Moheet, who notes that patients with a similar A1C can have very different glucose profiles. "Some patients have little variability in their before and after meal glucose and have rare hypoglycemic events, while others may have variability with high postmeal excursions and frequent hypoglycemia," he says. Therefore, identifying patients who might have a problem—and the reasons behind it—takes some detective work. What you can do:

- ***Ask the right questions.*** Dr. Moheet always asks if a patient has experienced low blood sugar and observed changes in its onset. For instance, a patient may have noticed they used to start perspiring and feeling on edge when levels dropped to 65 mg/dL, but now they don't notice symptoms until it dips to 55 mg/dL—a sign they may be developing hypoglycemia unawareness.

- ***Review medications.*** Common culprits of hypoglycemia include sulfonylureas, glinides and insulin. Also keep in mind that agents with a low risk of hypoglycemia, such as GLP-1 agonists and SGLT2 inhibitors, may contribute to hypoglycemia if combined with drugs known to cause it. And for patients treated with insulin, switching to a different type may help limit episodes of low blood sugar, notes Dr. Moheet. "Newer ultra-long-acting basal insulins may have a lower risk for hypoglycemia, especially overnight," he says.

- ***Consider testing beyond AIC.*** Although fingerstick self-monitoring can be helpful, many patients do not check their levels multiple times a day as recommended, says Kashif M. Munir, MD, Professor of Medicine (endocrinology) at University of Maryland School of Medicine. An alternative is continuous glucose monitoring (CGM), which is associated with improved AIC and reduction in hypoglycemia.[7,8] (To assess if a patient may benefit from CGM, see p. 24.) However, some patients are not interested in CGM, says Dr. Munir, noting that testing 1,5-AG (GlycoMark), an indicator of glycosuria, may offer additional benefit in identifying unrecognized glycemic excursions.

- ***Be alert to sudden changes in test results.*** While there could be various reasons for an abrupt dip in a patient's A1C, it may be a sign of recurrent hypoglycemia. "When we see a patient whose AIC had been on the high side, and all of a sudden it drops into the low 6s, right away I'm concerned," says Dr. Moheet. "It may be that they are just doing really well. But I will ask myself, *Is this patient having a lot of low blood sugar levels, and that's why their AIC suddenly looks so good?*"

- ***Look for dietary culprits.*** Patients whose blood sugar remains elevated following a meal may require a change in medication, though some may simply be consuming large amounts of carbohydrate; keeping a food diary may help identify this problem. On the other hand, patients who are skipping meals or eating too little may be setting themselves up for hypoglycemia, Dr. Moheet says. And some patients may adopt low-carb diets, which often result in low blood sugar after meals and requires adjustment of their medication to avoid overeating to prevent hypoglycemic events.

- ***Ask about activity levels.*** "I ask patients about exercise at every office visit," says Dr. Moheet. "It's very important for them to understand how physical activity affects their blood sugar." Based on type and duration of exercise some patients may require a carbohydrate snack before working out or need to modify their insulin regimen during or after exercising (e.g., taking less insulin before the next meal or adjusting the basal insulin rate on an insulin pump).

—by Timothy Gower

"IDENTIFYING PATIENTS WHO MIGHT HAVE A PROBLEM—AND THE REASONS BEHIND IT—MIGHT TAKE SOME DETECTIVE WORK."
—AMIR MOHEET, MD

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A FIRST-LINE OPTION FOR PATIENTS WITH TYPE 2 DIABETES OFFERING POWERFUL A1C REDUCTION[1]

WAKE UP TO THE POSSIBILITIES

For adults with type 2 diabetes

RYBELSUS®
semaglutide tablets 7mg | 14mg

THE FIRST TYPE 2 DIABETES PILL IN ITS CLASS (GLP-1 RA)[1]

ELIGIBLE PATIENTS PAY AS LITTLE AS $10 FOR A 1- TO 3-MONTH PRESCRIPTION[a]

To receive offer, 7 mg or 14 mg dose prescription must be for a 1-, 2-, or 3-month supply. For 3 mg dose, offer is limited to 1-month supply only.

GLP-1 RA=glucagon-like peptide-1 receptor agonist.

Indication and Usage

RYBELSUS® (semaglutide) tablets 7 mg or 14 mg is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

Limitations of Use

- RYBELSUS® has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis
- RYBELSUS® is not indicated for use in patients with type 1 diabetes

Important Safety Information

WARNING: RISK OF THYROID C-CELL TUMORS

- **In rodents, semaglutide causes dose-dependent and treatment-duration dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether RYBELSUS® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined**
- **RYBELSUS® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of RYBELSUS® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with RYBELSUS®**

Contraindications

- RYBELSUS® is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2), and in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in RYBELSUS®. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with RYBELSUS®

Warnings and Precautions

- **Risk of Thyroid C-Cell Tumors:** Patients should be further evaluated if serum calcitonin is measured and found to be elevated or thyroid nodules are noted on physical examination or neck imaging
- **Pancreatitis:** Has been reported in clinical trials. Observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, discontinue RYBELSUS® and initiate appropriate management; if confirmed, do not restart RYBELSUS®
- **Diabetic Retinopathy Complications:** In a pooled analysis of glycemic control trials with RYBELSUS®, patients reported diabetic retinopathy related adverse reactions during the trial (4.2% with RYBELSUS® and 3.8% with comparator). In a 2-year trial with semaglutide injection involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications occurred in patients treated with semaglutide injection (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline than among patients without a known history of diabetic retinopathy.

  Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy
- **Hypoglycemia:** Patients receiving RYBELSUS® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia
- **Acute Kidney Injury:** There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists, including semaglutide. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of RYBELSUS® in patients reporting severe adverse gastrointestinal reactions
- **Hypersensitivity:** Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with RYBELSUS®. If hypersensitivity reactions occur, discontinue use of RYBELSUS®, treat promptly per standard of care, and monitor until signs and symptoms resolve. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist
- **Acute Gallbladder Disease:** Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. In placebo-controlled trials, cholelithiasis was reported in 1% of patients treated with RYBELSUS® 7 mg. Cholelithiasis was not reported in RYBELSUS® 14 mg or placebo-treated patients. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated

Adverse Reactions

- Most common adverse reactions (incidence ≥5%) nausea, abdominal pain, diarrhea, decreased appetite, vomiting and constipation

Drug Interactions

- RYBELSUS® stimulates insulin release in the presence of elevated blood glucose concentrations. When initiating RYBELSUS®, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia
- RYBELSUS® delays gastric emptying and has the potential to impact the absorption of other oral medications. Closely follow RYBELSUS® administration instructions when coadministering with other oral medications and consider increased monitoring for medications with a narrow therapeutic index, such as levothyroxine

Study Designs

PIONEER 3: Head-to-Head vs Januvia®[1,2]

In a double-blind, double-dummy trial with a primary endpoint of mean change in A1C from baseline to 26 weeks, 1864 adult patients with type 2 diabetes on metformin alone or metformin with a sulfonylurea were randomized to RYBELSUS® 3 mg (n=466), RYBELSUS® 7 mg (n=465), RYBELSUS® 14 mg (n=465), or Januvia® 100 mg (n=467), all once daily.

- Confirmatory secondary endpoint: Mean change in body weight from baseline to 26 weeks

PIONEER 2: Head-to-Head vs Jardiance®[1,3]

In an open-label trial with a primary endpoint of mean change in A1C from baseline to 26 weeks, 822 adult patients with type 2 diabetes on metformin were randomized to RYBELSUS® 14 mg (n=411) or Jardiance® 25 mg (n=410), both once daily.

- Confirmatory secondary endpoint: Mean change in body weight from baseline to 26 weeks

Please see additional Important Safety Information in the Brief Summary of the Prescribing Information, including Boxed Warning, on the following pages.

[a]Offer available only to commercially insured patients with RYBELSUS® coverage. Month is defined as 30 days. Maximum savings of $300 per 1-month supply, $600 per 2-month supply, or $900 per 3-month supply. Eligibility and other restrictions apply.

IN SEPARATE HEAD-TO-HEAD STUDIES, RYBELSUS® DELIVERED SUPERIOR A1C REDUCTION VS JANUVIA® AND JARDIANCE®[1-3]

From baseline to Week 26

PIONEER 3: Compared to Januvia®, RYBELSUS® delivered

Superior A1C reductions[1,2]

Mean change in A1C **Primary endpoint**

RYBELSUS® 7 mg (n=465)	RYBELSUS® 14 mg (n=465)	JANUVIA® 100 mg (n=467)
-1.0% *p*<0.001 vs Januvia® (Baseline: 8.4%)	**-1.3%** *p*<0.001 vs Januvia® (Baseline: 8.3%)	**-0.8%** (Baseline: 8.3%)

Superior weight loss[1,2]

Mean change in body weight **Confirmatory secondary endpoint**

RYBELSUS® 7 mg (n=465)	RYBELSUS® 14 mg (n=465)	JANUVIA® 100 mg (n=467)
-4.8 lb ETD: -3.5 lb (95% CI: -4.4, -2.4) vs Januvia® (Baseline: 201 lb)	**-6.8 lb** ETD: -5.5 lb (95% CI: -6.6, -4.4) vs Januvia® (Baseline: 201 lb)	**-1.3 lb** (Baseline: 200 lb)

RYBELSUS® is not indicated for weight loss. See Study Design below.

ETD=estimated treatment difference.

PIONEER 2: Compared to Jardiance®, RYBELSUS® delivered

Superior A1C reductions[1,3]

Mean change in A1C **Primary endpoint**

RYBELSUS® 14 mg (n=411)	JARDIANCE® 25 mg (n=410)
-1.3% *p*<0.001 vs Jardiance® (Baseline: 8.1%)	**-0.9%** (Baseline: 8.1%)

See Study Design below.

Comparable weight loss[1,3]

Mean change in body weight **Confirmatory secondary endpoint**

RYBELSUS® 14 mg (n=411)	JARDIANCE® 25 mg (n=410)
-8.4 lb ETD: -0.2 lb (95% CI: -1.5, 1.1) vs Jardiance® (Baseline: 202 lb)	**-8.1 lb** (Baseline: 201 lb)

To learn more, visit **RYBELSUSpro.com**

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RYBELSUS® semaglutide tablets 7mg | 14mg

RYBELSUS® (semaglutide) tablets

Rx Only

BRIEF SUMMARY: Please consult package insert for full prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS: In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether RYBELSUS® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions]*. RYBELSUS® is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Contraindications]*. Counsel patients regarding the potential risk for MTC with the use of RYBELSUS® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with RYBELSUS® *[see Contraindications and Warnings and Precautions]*.

INDICATIONS AND USAGE: RYBELSUS® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitations of Use: RYBELSUS® has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis *[see Warnings and Precautions]*. RYBELSUS® is not indicated for use in patients with type 1 diabetes mellitus.

CONTRAINDICATIONS: RYBELSUS® is contraindicated in patients with: A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Warnings and Precautions]*. A prior serious hypersensitivity reaction to semaglutide or to any of the excipients in RYBELSUS®. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with RYBELSUS® *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-Cell Tumors: In mice and rats, semaglutide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures. It is unknown whether RYBELSUS® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined. Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans. RYBELSUS® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of RYBELSUS® and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with RYBELSUS®. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly 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 further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated. **Pancreatitis:** In glycemic control trials, pancreatitis was reported as a serious adverse event in 6 RYBELSUS®-treated patients (0.1 events per 100 patient years) versus 1 in comparator-treated patients (<0.1 events per 100 patient years). After initiation of RYBELSUS®, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, RYBELSUS® should be discontinued and appropriate management initiated; if confirmed, RYBELSUS® should not be restarted. **Diabetic Retinopathy Complications:** In a pooled analysis of glycemic control trials with RYBELSUS®, patients reported diabetic retinopathy related adverse reactions during the trial (4.2% with RYBELSUS® and 3.8% with comparator). In a 2-year cardiovascular outcomes trial with semaglutide injection involving patients with type 2 diabetes and high cardiovascular risk, diabetic retinopathy complications (which was a 4 component adjudicated endpoint) occurred in patients treated with semaglutide injection (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (semaglutide injection 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (semaglutide injection 0.7%, placebo 0.4%). Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy. **Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin:** Patients receiving RYBELSUS® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia *[see Adverse Reactions and Drug Interactions]*. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. **Acute Kidney Injury:** There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists, including semaglutide. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of RYBELSUS® in patients reporting severe adverse gastrointestinal reactions. **Hypersensitivity:** Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with RYBELSUS®. If hypersensitivity reactions occur, discontinue use of RYBELSUS®; treat promptly per standard of care, and monitor until signs and symptoms resolve. RYBELSUS® is contraindicated in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in RYBELSUS®. *[see Adverse Reactions]*. Anaphylaxis and angioedema have been reported with GLP-1 receptor agonists. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to anaphylaxis with RYBELSUS®. **Acute Gallbladder Disease:** Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. In placebo-controlled trials, cholelithiasis was reported in 1% of patients treated with RYBELSUS® 7 mg. Cholelithiasis was not reported in RYBELSUS® 14 mg or placebo-treated patients. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated *[see Adverse Reactions]*.

ADVERSE REACTIONS: The following serious adverse reactions are described below or elsewhere in the prescribing information: Risk of Thyroid C-cell Tumors *[see Warnings and Precautions];* Pancreatitis *[see Warnings and Precautions];* Diabetic Retinopathy Complications *[see Warnings and Precautions];* Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin *[see Warnings and Precautions];* Acute Kidney Injury *[see Warnings and Precautions];* Hypersensitivity *[see Warnings and Precautions];* Acute Gallbladder Disease *[see Warnings and Precautions]*. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Pool of Placebo-Controlled Trials: The data in Table 1 are derived from 2 placebo-controlled trials in adult patients with type 2 diabetes. These data reflect exposure of 1071 patients to RYBELSUS® with a mean duration of exposure of 41.8 weeks. The mean age of patients was 58 years, 3.9% were 75 years or older and 52% were male. In these trials, 63% were White, 6% were Black or African American, and 27% were Asian; 19% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes for an average of 9.4 years and had a mean HbA_{1c} of 8.1%. At baseline, 20.1% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR ≥90 mL/min/1.73m^2) in 66.2%, mildly impaired (eGFR 60 to 90 mL/min/1.73m^2) in 32.4% and moderately impaired (eGFR 30 to 60 mL/min/1.73m^2) in 1.4% of patients. Pool of Placebo- and Active-Controlled Trials: The occurrence of adverse reactions was also evaluated in a larger pool of adult patients with type 2 diabetes participating in 9 placebo- and active-controlled trials. In this pool, 4116 patients with type 2 diabetes were treated with RYBELSUS® for a mean duration of 59.8 weeks. The mean age of patients was 58 years, 5% were 75 years or older and 55% were male. In these trials, 65% were White, 6% were Black or African American, and 24% were Asian; 15% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes for an average of 8.8 years and had a mean HbA_{1c} of 8.2%. At baseline, 16.6% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR ≥90 mL/min/1.73m^2) in 65.9%, mildly impaired (eGFR 60 to 90 mL/min/1.73m^2) in 28.5%, and moderately impaired (eGFR 30 to 60 mL/min/1.73m^2) in 5.4% of the patients. Common Adverse Reactions: Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of RYBELSUS® in adult patients with type 2 diabetes in the pool of placebo-controlled trials. These adverse reactions occurred more commonly on RYBELSUS® than on placebo and occurred in at least 5% of patients treated with RYBELSUS®.

Table 1. Adverse Reactions in Placebo-Controlled Trials Reported in ≥5% of RYBELSUS®-Treated Patients with Type 2 Diabetes Mellitus

Adverse Reaction	Placebo (N=362) %	RYBELSUS® 7 mg (N=356) %	RYBELSUS® 14 mg (N=356) %
Nausea	6	11	20
Abdominal Pain	4	10	11
Diarrhea	4	9	10
Decreased appetite	1	6	9
Vomiting	3	6	8
Constipation	2	6	5

In the pool of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1.

Gastrointestinal Adverse Reactions: In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving RYBELSUS® than placebo (placebo 21%, RYBELSUS® 7 mg 32%, RYBELSUS® 14 mg 41%). The majority of reports of nausea, vomiting, and/or diarrhea occurred during dose escalation. More patients receiving RYBELSUS® 7 mg (4%) and RYBELSUS® 14 mg (8%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (1%). In addition to the reactions in Table 1, the following gastrointestinal adverse reactions with a frequency of <5% were associated with RYBELSUS® (frequencies listed, respectively, as placebo; 7 mg; 14 mg): abdominal distension (1%, 2%, 3%), dyspepsia (0.6%, 3%, 0.6%), eructation (0%, 0.6%, 2%), flatulence (0%, 2%, 1%), gastroesophageal reflux disease (0.3%, 2%, 2%), and gastritis (0.8%, 2%, 2%). Other Adverse Reactions: *Pancreatitis:* In the pool of placebo- and active-controlled trials with RYBELSUS®, pancreatitis was reported as a serious adverse event in 6 RYBELSUS®-treated patients (0.1 events per 100 patient years) versus 1 in comparator-treated patients (<0.1 events per 100 patient years). *Diabetic Retinopathy Complications:* In the pool of placebo- and active-controlled trials with RYBELSUS®, patients reported diabetic retinopathy related adverse reactions during the trial (4.2% with RYBELSUS® and 3.8% with comparator). *Hypoglycemia:* Table 2 summarizes the incidence of hypoglycemia by various definitions in the placebo-controlled trials.

Table 2. Hypoglycemia Adverse Reactions in Placebo-Controlled Trials In Patients with Type 2 Diabetes Mellitus

	Placebo	RYBELSUS® 7 mg	RYBELSUS® 14 mg
Monotherapy			
(26 weeks)	**N=178**	**N=175**	**N=175**
Severe*	0%	1%	0%
Plasma glucose <54 mg/dL	1%	0%	0%
Add-on to metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin in patients with moderate renal impairment			
(26 weeks)	**N=161**	**–**	**N=163**
Severe*	0%	–	0%
Plasma glucose <54 mg/dL	3%	–	6%
Add-on to insulin with or without metformin			
(52 weeks)	**N=184**	**N=181**	**N=181**
Severe*	1%	0%	1%
Plasma glucose <54 mg/dL	32%	26%	30%

*"Severe" hypoglycemia adverse reactions are episodes requiring the assistance of another person.

Hypoglycemia was more frequent when RYBELSUS® was used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. *Increases in Amylase and Lipase:* In placebo-controlled trials, patients exposed to RYBELSUS® 7 mg and 14 mg had a mean increase from baseline in amylase of 10% and 13%, respectively, and lipase of 30% and 34%, respectively. These changes were not observed in placebo-treated patients. *Cholelithiasis:* In placebo-controlled trials, cholelithiasis was reported in 1% of patients treated with RYBELSUS® 7 mg. Cholelithiasis was not reported in RYBELSUS® 14 mg or placebo-treated patients. *Increases in Heart Rate:* In placebo-controlled trials, RYBELSUS® 7 mg and 14 mg resulted in a mean increase in heart rate of 1 to 3 beats per minute. There was no change in heart rate in placebo-treated patients. **Postmarketing Experience:** The following adverse reactions have been reported during post-approval use of semaglutide, the active ingredient of RYBELSUS®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Gastrointestinal:* ileus; *Hypersensitivity:* anaphylaxis, angioedema, rash, urticaria; *Hepatobiliary:* cholecystitis, cholelithiasis requiring cholecystectomy

DRUG INTERACTIONS: Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin: RYBELSUS® stimulates insulin release in the presence of elevated blood glucose concentrations. Patients receiving RYBELSUS® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. When initiating RYBELSUS®, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions and Adverse Reactions]*. **Oral Medications:** RYBELSUS® causes a delay of gastric emptying, and thereby has the potential to impact the absorption of other oral medications. Levothyroxine exposure was increased 33% (90% CI: 125-142) when administered with RYBELSUS® in a drug interaction study. When coadministering oral medications instruct patients to closely follow RYBELSUS® administration instructions. Consider increased clinical or laboratory monitoring for medications that have a narrow therapeutic index or that require clinical monitoring.

USE IN SPECIFIC POPULATIONS: Pregnancy: Risk Summary: Available data with RYBELSUS® use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy *(see Clinical Considerations)*. Based on animal reproduction studies, there may be potential risks to the fetus from exposure to RYBELSUS® during pregnancy. RYBELSUS® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In pregnant rats administered semaglutide during organogenesis, embryofetal mortality, structural abnormalities and alterations to growth occurred at maternal exposures below the maximum recommended human dose (MRHD) based on AUC. In rabbits and cynomolgus monkeys administered semaglutide during organogenesis, early pregnancy losses and structural abnormalities were observed at exposure below the MRHD (rabbit) and ≥10-fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species *(see Data)*. The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA_{1c} >7 and has been reported to be as high as 20–25% in women with a HbA_{1c} >10. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Clinical Considerations: *Disease associated maternal and fetal risk:* Poorly controlled diabetes during pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity. Data: *Animal Data:* In a combined fertility and embryofetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.2-, 0.7-, and 2.1-fold the MRHD) were administered to males for 4 weeks prior to and throughout mating and to females for 2 weeks prior to mating, and throughout organogenesis to Gestation Day 17. In parental animals, pharmacologically mediated reductions in body weight gain and food consumption were observed at all dose levels. In the offspring, reduced growth and fetuses with visceral (heart blood vessels) and skeletal (cranial bones, vertebra, ribs) abnormalities were observed at the human exposure. In an embryofetal development study in pregnant rabbits, subcutaneous doses of 0.0010, 0.0025 or 0.0075 mg/kg/day (0.06-, 0.6-, and 4.4-fold the MRHD) were administered throughout organogenesis from Gestation Day 6 to 19. Pharmacologically mediated reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternebra) fetal abnormalities were observed at ≥0.0025 mg/kg/day, at clinically relevant exposures. In an embryofetal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (1.9-, 9.9-, and 29-fold the MRHD) were administered throughout organogenesis, from Gestation Day 16 to 50. Pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternebra, ribs) at ≥0.075 mg/kg twice weekly (≥9X human exposure). In a pre- and postnatal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (1.3-, 6.4-, and 14-fold the MRHD) were administered from Gestation Day 16 to 140. Pharmacologically mediated marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with an increase in early pregnancy losses and led to delivery of slightly smaller offspring at ≥0.075 mg/kg twice weekly (≥6X human exposure). Salcaprozate sodium (SNAC), an absorption enhancer in RYBELSUS®, crosses the placenta and reaches fetal tissues in rats. In a pre- and postnatal development study in pregnant Sprague Dawley rats, SNAC was administered orally at 1,000 mg/kg/day (exposure levels were not measured) on Gestation Day 7 through lactation day 20. An increase in gestation length, an increase in the number of stillbirths and a decrease in pup viability were observed. **Lactation:** Risk Summary: There are no data on the presence of semaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. Semaglutide was present in the milk of lactating rats. SNAC and/or its metabolites concentrated in the milk of lactating rats. When a substance is present in animal milk, it is likely that the substance will be present in human milk *(see Data)*. There are no data on the presence of SNAC in human milk. Since the activity of UGT2B7, an enzyme involved in SNAC clearance, is lower in infants compared to adults, higher SNAC plasma levels may occur in neonates and infants. Because of the unknown potential for serious adverse reactions in the breastfed infant due to the possible accumulation of SNAC from breastfeeding and because there are alternative formulations of semaglutide that can be used during lactation, advise patients that breastfeeding is not recommended during treatment with RYBELSUS®. Data: In lactating rats, semaglutide was detected in milk at levels 3-12 fold lower than in maternal plasma. SNAC and/or its metabolites were detected in milk of lactating rats following a single maternal administration on lactation day 10. Mean levels of SNAC and/or its metabolites in milk were approximately 2-12 fold higher than in maternal plasma. **Females and Males of Reproductive Potential:** Discontinue RYBELSUS® in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide *[see Use in Specific Populations]*. **Pediatric Use:** The safety and effectiveness of RYBELSUS® have not been established in pediatric patients. **Geriatric Use:** In the pool of glycemic control trials, 1229 (30%) RYBELSUS®-treated patients were 65 years of age and over and 199 (5%) RYBELSUS®-treated patients were 75 years of age and over. In PIONEER 6, the cardiovascular outcomes trial, 891 (56%) RYBELSUS®-treated patients were 65 years of age and over and 200 (13%) RYBELSUS®-treated patients were 75 years of age and over. No overall differences in safety or effectiveness for RYBELSUS® have been observed between patients 65 years of age and older and younger adult patients. **Renal Impairment:** The safety and effectiveness of RYBELSUS® was evaluated in a 26-week clinical study that included 324 patients with moderate renal impairment (eGFR 30 to 59 mL/min/1.73m^2). In patients with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in semaglutide pharmacokinetics (PK) was observed. No dose adjustment of RYBELSUS® is recommended for patients with renal impairment. **Hepatic Impairment:** In a study in subjects with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics (PK) was observed. No dose adjustment of RYBELSUS® is recommended for patients with hepatic impairment.

OVERDOSAGE: In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of RYBELSUS® of approximately 1 week.

More detailed information is available upon request.

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Date of Issue: 01/2023; Version: 5

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PATENT INFORMATION:
http://www.novonordisk-us.com/products/product-patents.html

 US22RYB01075 1/2023

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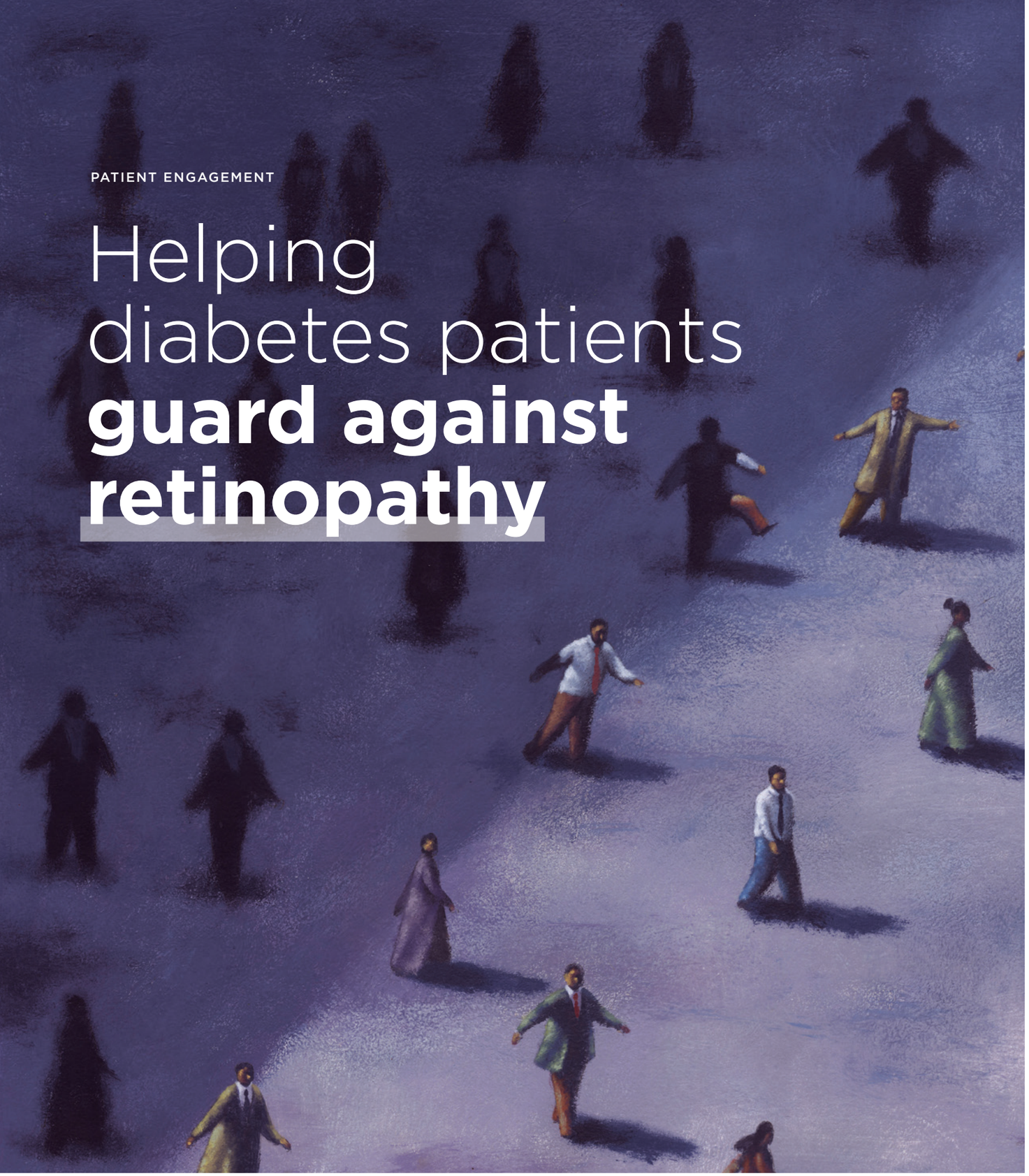
RYBELSUS® semaglutide tablets 7mg | 14mg



PATIENT ENGAGEMENT

Helping diabetes patients **guard against retinopathy**

Illustration by James Fryer

Despite recent medical advances, retinopathy continues to strike patients with type 2 diabetes. Here, experts discuss ways to prevent blindness by stopping the disease in its tracks.

Retinopathy affects an estimated 30% to 40% of people with diabetes and remains the leading cause of blindness in working-age adults, according to the CDC.[1,2] "When you talk about what people with diabetes are most fearful of, losing their eyesight is right up there," says Robert A. Gabbay, MD, PhD, FACP, Chief Scientific and Medical Officer at the American Diabetes Association (ADA). And while most people with type 2 diabetes are aware that their condition can affect their eye health, clinicians are still finding it difficult to prevent the disease. "There have been many advances over the last several years so that most cases of blindness can be avoided," says Dr. Gabbay. "And yet loss of sight continues to happen."

There are a variety of barriers to preventive optical care that increase the likelihood of developing retinopathy and its associated complications. Here are strategies to overcome these challenges to preserving eyesight in individuals with type 2 diabetes.

Prioritize patient education about eye exams.

Although most people with diabetes understand the potential effects on their eye health, many are unsure about how to approach preventive care for retinopathy. "It's about catching the disease early when it's asymptomatic," says Dr. Gabbay. To this end, the ADA guidelines recommend that people with type 2 diabetes have their first dilated eye exam at the time of diagnosis; if there is no evidence of retinopathy during the first exam and glycemia is well controlled, the ADA recommends screening every 1 to 2 years; and if there is any level of retinopathy, people with diabetes should have eye exams at least annually.[3] People with risk factors, such as a longer duration of diabetes and existing retinopathy, should be screened more frequently.[3] Additionally, both the ADA and the American Academy of Ophthalmology (AAO) recommend that all individuals with diabetes receive at least annual eye exams, even in the absence of vision problems.[4]

"The real challenge is that only roughly half of people with diabetes get a yearly eye exam," says Dr. Gabbay.[5] He notes that, in many of these cases, patients are unaware that their eyesight should be evaluated because they're not having vision problems. "If people wait to be seen until there's a change in their vision, it's often too late by then."

Mihail Zilbermint, MD, MBA, FACE, an Associate Professor at Johns Hopkins University School of Medicine, echoes these concerns. "Most of my patients are hospitalized for reasons other than diabetes, so eye health may not be their priority," Dr. Zilbermint says. "Once I address the main problem, which is usually related to glycemic control, I tell them that retinopathy often presents without symptoms in its early stages and encourage them to make an eye exam appointment." He also says he tells these patients: "If you have one microvascular complication of diabetes, like nephropathy, odds are that you may have another complication as well."

Dr. Gabbay adds that some patients may be confused about what type of eye exam is needed. "Screening does not mean getting checked for glasses—that's where the disconnect is," he says, adding that dilation or retinal imaging is required to truly evaluate retinal health with diabetes, and patients may not understand the difference in these types of exams.

"Clinicians should prioritize patient education about the importance of comprehensive diabetes management, including regular eye screenings, to prevent complications like retinopathy due to diabetes," says Dr. Zilbermint. He suggests clinicians use resources from the

ADA (*ada.org*) to help support these efforts.

Dr. Gabbay also encourages clinicians to leverage technology—such as e-chart reminders and text messaging—to help patients keep track of when their annual exams may be due. Likewise, Dr. Zilbermint suggests adding information about diabetes eye exam recommendations in the outpatient notes template on patient records.

Help them gain access to care.

Barriers to healthcare contribute to an increased risk for eye disease for socioeconomically vulnerable populations. Minority populations are, on average, 2 to 3 times more likely to develop vision-related complications of type 2 diabetes (see sidebar, *below*).[6] "Patients with lower socioeconomic status often face additional challenges in accessing healthcare services, including eye care," Dr. Zilbermint says. These may include financial barriers, limited specialist availability in their area or logistical challenges.[7] "For many of my patients, managing diabetes and its complications can be difficult, particularly for those with limited access to healthcare resources or who face economic hardships," he says. "Even those who have health insurance may have a high deductible and try to avoid doctors or stretch out medications."

To address these disparities, Dr. Zilbermint emphasizes the need for healthcare organizations to collaborate with community partners to help increase access to eye care and improve optical outcomes. "Here, at Johns Hopkins Medicine, we organize community events and collaborate with other healthcare partners," he says. "Mobile medicine or community-based screening programs and financial assistance for treatment are crucial in addressing these disparities."

Dr. Gabby notes that sometimes these communities may have trust issues with healthcare professionals. "Building connections with community health partners is an important way to help patients overcome barriers to eye care and ensure they can access the care they need," Dr. Gabby says. "Community health workers can act as an important bridge for patients to navigate the medical system and identify resources available to them," he says.

"Mobile health applications can also improve access to care for patients who face geographical or socioeconomic barriers," notes Dr. Zilbermint. "The good news is that dilatation screening doesn't need to be done by an ophthalmologist, which there are fewer of," adds Dr. Gabbay. "It can be done by an optometrist as well, of which there are many more available."

Optimize glycemic control.

Poor glycemic control is an important risk factor for the development and progression of retinopathy in patients with type 2 diabetes.[8] Clinicians can support patients by emphasizing key steps toward achieving glycemic control, including monitoring patients with regular checkups and follow-up visits, encouraging appropriate lifestyle changes, and prescribing medications as needed. Medical management of diabetes risk may involve the use of glucose-lowering medications as well as blood pressure and lipid-lowering therapies, which can also impact eye health.[3]

Interestingly, preliminary evidence suggests GLP-1 receptor agonists may have some benefit for lowering not only A1C but also the risk for retinopathy, although long-term studies are needed to confirm if there's a benefit.[9,10] "Any diabetes medication that lowers glucose into a healthier range is helpful and should be considered," says Dr. Gabbay. The ADA recommends evaluating eye health before initiating such therapies, though, as rapid reductions in glucose levels has been linked to worsening of retinopathy.[3,11]

Ultimately, Dr. Gabbay says, the messaging to patients should focus on the actionable steps they can take to prevent retinopathy and the importance of eye care. "Tell your patients: 'You don't need to lose vision because of diabetes—there are treatments, and you just have to catch it early. Getting yearly eye exams can help you save your eyesight.'" ●

—by Morgan Meissner

"CLINICIANS SHOULD PRIORITIZE PATIENT EDUCATION ABOUT THE IMPORTANCE OF COMPREHENSIVE DIABETES MANAGEMENT, INCLUDING REGULAR EYE SCREENINGS."
—MIHAIL ZILBERMINT, MD, MBA, FACE

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Overcoming racial disparities in diabetes eye care

A variety of disparities continue to exist in diabetes eye care that compromise outcomes for minority populations. According to results from a 9-year study involving patients with diabetes at the Johns Hopkins Wilmer Eye Institute, Black and Hispanic patients were 24% and 26% more likely, respectively, than their White counterparts to experience lapses in eye care, including screening and follow-up.[7]

A 2023 study involving participants with diabetes and retinopathy conducted by the National Institutes of Health's All of Us Research Program, found that compared with White patients, Black patients were more than twice as likely to report:[12]

- Being treated with less respect
- Being treated with less courtesy
- Receiving poorer service than other people.

Fortunately, acknowledgment of the problem and potential solutions are being developed by diabetes researchers. Robert A. Gabbay, MD, PhD, FACP, Chief Scientific and Medical Officer at the American Diabetes Association (ADA), says the ADA is currently engaged in a variety of projects to improve health equity in diabetes care, including issues related to eye health, through the activation of community resources and education of community health partners. More information about those efforts can be found on the ADA's Collaboration for Equitable Health website (*diabetes.org/about-us/health-equity-commitment*).

Mihail Zilbermint, MD, MBA, FACE, an Associate Professor at Johns Hopkins University School of Medicine, also encourages clinicians to be mindful of the language they use to avoid stigmatization and improve connections with vulnerable patients living with diabetes.[13] He advises against the use of the word "diabetic," which can be seen as a stigmatizing and restricting label to many patients. He notes that clinicians should also use care when discussing overweight and obesity, which are common among people with diabetes but can arouse feelings of blame and stereotyping.[13]

PATIENT: SETH, 63, WAS DIAGNOSED WITH TYPE 2 DIABETES 20 YEARS AGO. HE ALSO HAD DYSLIPIDEMIA, HYPERTENSION AND CORONARY ARTERY DISEASE.

"Seth lost 30 lbs. in 3 months"

PHYSICIAN:

Betul Hatipoglu, MD

Professor of Medicine, CWRU School of Medicine, Vice Chair, UH System Clinical Affairs, Medical Director, Diabetes & Metabolic Care Center, Mary B. Lee Chair in Adult Endocrinology University Hospital Cleveland Medical Center

History:
I saw Seth, 63, who was diagnosed with type 2 diabetes when he was in his 40s. At first he managed it with diet and exercise, but when that was no longer effective, he went on metformin, which worked for a few years. As his disease progressed, he started on a DPP4 inhibitor and pioglitazone but his A1C continued to rise so he needed to be on insulin up to 20 units daily. What's more, in the last 3 years, Seth started developing signs of cardiovascular disease. He had an abnormal stress test, and he had a stent placed after a cardio cath found a blockage. He was given statin therapy and put on ACE inhibitors for blood pressure management. His primary care physician, who referred him to me, was concerned about his A1C (9.1%) and gave him a continuous glucose monitor (CGM). Fortunately, when the cardiologist saw him for his dyslipidemia, hypertension and CAD, Seth was started on an SGLT2 inhibitor.

Initiating treatment:
On his initial visit with me, we discussed his CGM which had a target range of 56%, and his BMI which was 30. We decided to keep him on his medications but discontinue the DPP-4 inhibitor and add a GLP-1 receptor agonist (GLP-1 RA). I explained that the GLP-1 RA would help with his weight, cardiovascular risk and kidneys. I told him that if he responded well to this medication and if he lost some weight, he might be able to stop his insulin because the requirement wasn't that high. I explained the potential GI side effects of GLP-1 RAs, which I'd seen in some other patients.

> "We need to make sure they take the medication that benefits them the most."

Seth started taking the added medication, and we titrated up. Within the first 3 months, he lost almost 30 lbs., his hemoglobin came down to 6.6% and his CGM was in the 94% target range. I emphasized that he also had to make lifestyle modifications, including diet and exercise, because medication alone wouldn't do the trick. Seth was extremely pleased with the results, and we were able to decrease the insulin and eventually stop the other medications.

Considerations:
This case illustrates how clinicians need to go back and evaluate their patients' medications; even if the patient is being well controlled, we need to make sure they are taking the medication that will benefit them most. I make sure to evaluate my patients' medication list and give them the benefit of some of the newest drugs in our toolbox, such as a GLP-1 RA or an SGLT2 inhibitor.

NEW!
KOL ON DEMAND VIDEO
Scan here for more insight on Seth's case.

Illustrations by Juhee Kim

PATIENT: JANET, 58, HAD A 5-YEAR HISTORY OF DIABETES. SHE WAS ALSO TAKING MEDICATIONS FOR HYPERTENSION AND DYSLIPIDEMIA.

"Shared decision-making was key for reaching her goals"

History:
Janet was referred to me by her PCP. At her initial exam, her BMI was 26.9, A1C was 7.9% and her blood pressure was stable at 126/68. Her labs also revealed that she had stage 2 chronic kidney disease with moderately increased albuminuria (eGFR 62 mL/min and UACR 146 mg/g creatinine). Her diabetes medications included metformin twice a day and glipizide once a day. She had tried a GLP-1 receptor agonist (GLP-1 RA) but could not tolerate the GI side effects of nausea with dyspepsia regardless of the dose. Her PCP discussed adding a medication from the SGLT2 inhibitor class, but Janet was hesitant due to concern about developing a yeast infection, which is commonly associated with this. Her kidneys weren't doing well and her UACR was higher now than it was 3 months ago. Unsure of what else to do, her PCP referred Janet to me with the hope that I could assist her with finding the optimal treatment regimen.

Initiating treatment:
Janet and I spent a great deal of time discussing her concerns regarding both her diabetes as well as the medications used to treat it. I acknowledged that what she understood about the increased risk for a genital mycotic infection was accurate but clarified that not every person who takes an SGLT2 inhibitor will develop a problem. We discussed the additional risk factors that would make her more susceptible to infection (such as a history of urinary tract infections, overactive bladder and incontinence), all of which she reported not having.

We also discussed the importance of adequate hydration, avoiding foods and beverages that would cause a significant rise in her glucose and thus would increase the amount of glucose in her urine. Importantly, we discussed the benefit of this medication for her kidney health and the growing evidence that SGLT2 inhibitors reduce albuminuria and slow the progression to end-stage kidney disease. Janet agreed to try it, and we discontinued her glipizide to prevent the risk of hypoglycemia. Janet reported walking 30 minutes nearly every day, and I urged her to continue doing so. I also encouraged her to replace her sugar-sweetened coffee with a product that is calorie-free and less likely to spike her glucose, which would reduce the amount of glucosuria and facilitate weight loss. I reinforced the importance of maintaining an optimal weight as well as controlling her high blood pressure and high cholesterol, as these also contribute to progression of kidney disease.

After 3 months, her weight was down about 8 lbs. (BMI of 25.7), her blood pressure was 126/74, her A1C was 6.4% and her kidney markers improved. Her eGFR was now 68 mL/min and her UACR was 78 mg/g creatinine. She was pleased that her kidney health was improving without experiencing side effects. Janet also was willing to retry a GLP-1 RA in the future if needed, as the changes in her diet would make her more likely to tolerate it.

Considerations:
Janet's case exemplifies the value of shared decision-making. Discussing the risks and benefits of a medication and explaining what would increase and possibly mitigate the risk empowers patients and builds a trusting rapport with their healthcare providers, which is vital for optimal management of a patient's cardiometabolic diseases and their related complications. Optimal management of any chronic and progressive disease goes beyond prescribing a medication. It involves managing all associated comorbidities with lifestyle interventions as well as appropriate pharmacotherapy. ●

NURSE PRACTITIONER:

Lucia M. Novak, MSN, ANPBC, BCADM

President of Diabesity, LLC, and Co-executive Director of Capital Health Metabolic & Weight Loss Center, Silver Spring, MD

Q

A

Expert insight on diabetes management

Illustration by Yoko Baum / Ikon Images

Making dietary changes doable

Q: How do you counsel newly diagnosed patients about making dietary changes?

A: Dietary and lifestyle adjustments serve as the cornerstone of effective diabetes management. I prioritize understanding the patient's food preferences and habits, using this insight to guide our discussion. While I strongly advocate involving a registered nutritionist in personalized meal planning, initiating the conversation and stressing its importance is crucial. I emphasize promoting healthy eating habits, with a focus on substituting nutrient-dense foods with those that are highly processed and loaded with simple carbs and saturated fats. Instead, I encourage the inclusion of complex carbs, polyunsaturated and monounsaturated fats and protein into their diet. It's essential to tailor nutritional guidance to each patient's unique circumstances, considering factors such as cultural background, health literacy and readiness for behavioral changes. This individualized approach ensures practical and sustainable recommendations.

I strive to ensure that patients enjoy their meals and derive pleasure from eating, while also recognizing that structured meal planning may benefit some individuals. Understanding a patient's history, previous trials and dietary habits helps determine the most successful strategy for achieving their goals. Adopting a personalized approach increases the likelihood of sustained dietary changes and improved diabetes management outcomes.

Preventing hypoglycemia

Q: How do you help patients avoid hypoglycemia?

A: I review the patient's history of hypoglycemia, including their risk factors and previous episodes they may have experienced. When selecting diabetes medications and setting glycemic goals, I consider each patient's risk for hypoglycemia. This ensures that treatment plans are tailored to the individual's unique needs and minimizes the risk of low blood glucose levels. For example, newer medication classes such as GLP-1 receptor agonists and SGLT2 inhibitors are less likely to cause hypoglycemia than sulfonylureas or insulin. For individuals at high risk for hypoglycemia, I recommend the use of continuous glucose monitoring as it provides real-time feedback on blood sugar levels, allowing for early detection and intervention to prevent hypoglycemic events.

Additionally, I prescribe glucagon for all individuals taking insulin or at high risk for hypoglycemia, as recommended. It's also important to educate family members, caregivers and coworkers on the location and administration of glucagon in case of severe hypoglycemia requiring emergency intervention.

Improving adherence

Q: How do you help patients overcome adherence issues?

A: Patients who juggle multiple responsibilities at work and home can forget to take their medication. Additionally, unpleasant side effects such as hypoglycemia, gastrointestinal issues and nonspecific symptoms like fatigue can discourage patients from sticking to their medications.

When I learn that my patients are not following their regimen, I try first to identify the cause. Sometimes it takes a simple strategy such as setting reminders on their phone. Exploring cost-saving options like generic alternatives or patient assistance programs can help address financial constraints. To avoid discontinuation related to side effects, it's important to mitigate side effects through dosage adjustments or switch to alternative medications. Equally important is educating patients about side effects and setting expectations.

Various interventions, including telemedicine, automated reminders and motivational interviewing can be utilized to increase adherence. Healthcare providers play a vital role in identifying barriers specific to diabetes management and directing patients to resources and support services tailored to their needs. By providing patient-centered care, healthcare teams can support patients in achieving treatment success and reducing the risk of complications. Additionally, it's crucial to empower patients to manage their health. This involves empathetic counseling on dietary and lifestyle modifications specifically tailored to diabetes management, emphasizing the significant impact such changes can have on blood glucose and their overall health.

Counseling on CVD risk

Q: How do you educate patients about the importance of managing cardiovascular risk factors?

A: When patients come to see me, I make a point to engage them in conversations about cardiovascular risk reduction with a personalized touch. I emphasize that managing cardiovascular risk factors is not just about controlling blood glucose levels—it's about looking at the bigger picture of their overall health. I approach our discussions by first stratifying their cardiovascular disease (CVD) risk, considering factors like blood pressure, cholesterol levels, smoking history, physical activity and family history of heart disease. This holistic assessment allows us to understand their risk profile comprehensively.

During our conversation, I stress the importance of addressing all modifiable risk factors together rather than focusing solely on glucose management. I explain that by managing factors like blood pressure, cholesterol and lifestyle habits, we can significantly reduce their risk of developing heart disease and other cardiovascular complications. Using this comprehensive approach, we work together to develop a personalized plan that prioritizes cardiovascular health while also addressing their diabetes management needs. This collaborative process empowers patients to actively participate in their care and make informed decisions that support their overall well-being.

OUR EXPERT
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Cover illustration by Brian Stauffer

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Clinician Update

EXAM TOOL

Screening for "Diabetes Distress"

Research shows that up to 40% of patients with type 2 diabetes exhibit signs of diabetes distress, a condition marked by feelings of frustration and anxiety related to managing their disease. For many, this comes with not only physical but also mental challenges that can lower their quality of life and affect diabetes outcomes. To determine if your patients are experiencing distress, consider using a questionnaire such as the following:

On a scale of 1-5, with 1 being "not a problem" and 5 being a "very serious problem," how would you rate the following? (circle each answer)

1.	I feel burned out by all the attention and effort that diabetes demands of me.	1	2	3	4	5
2.	It bothers me that diabetes seems to control my life.	1	2	3	4	5
3.	I'm frustrated that even when I do what I am supposed to for my diabetes, it doesn't seem to make a difference.	1	2	3	4	5
4.	I worry about having a serious low glucose event when I'm alone.	1	2	3	4	5
5.	I am so tired of having to worry about diabetes all the time.	1	2	3	4	5
6.	When it comes to my diabetes, I often feel like a failure.	1	2	3	4	5
7.	I often feel ashamed or embarrassed when other people know about my diabetes.	1	2	3	4	5
8.	Living with diabetes is overwhelming for me.	1	2	3	4	5
9.	It bothers me that I don't get as much exercise as I should.	1	2	3	4	5
10.	I can't escape this sinking feeling that diabetes is eventually going to get me.	1	2	3	4	5

SCORING

(add all circled numbers and divide by 10)

- Mean score <2.0 indicates little or no distress.
- Mean score between 2 and 2.9 indicates moderate distress.
- Mean score >3.0 indicates significant distress.

Note: This tool is based on the 29-question Type 2 Diabetes Distress Assessment System by the Diabetes Distress Assessment and Resource Center. For the complete questionnaire, visit *diabetesdistress.org*.