Health Monitor®

Clinician Update

Type 2 Diabetes Management

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Content reviewed by:

AACE®

MANAGING CORONARY DISEASE IN PATIENTS WITH DIABETES

The latest AHA/ACC guideline offers new strategies for multidisciplinary care.

Research shows that many patients with type 2 diabetes also have chronic coronary disease (CCD)—be it angina, coronary artery disease or ischemic heart disease.[1-3] And the stakes for avoiding subsequent complications are high: About 8 in 10 patients with diabetes die from an ischemic or other CV-related cause.[4]

Many providers find managing both diseases concurrently to be difficult in their day-to-day practice. "Often the focus can shift to where the physician is thinking about one risk over the other," says Gregg C. Fonarow, MD, interim chief of UCLA's Division of Cardiology and Director of the Ahmanson-UCLA Cardiomyopathy Center in Los Angeles. "If the focus becomes just the A1C and not decreasing the patient's risk of a coronary event, this may result in a less optimal regimen for the patient."

Polypharmacy is another potential pitfall, according to Dr. Fonarow. Patients with CCD and diabetes take multiple medications to manage both conditions, and some patients have additional comorbidities that require still more therapies. When this is the case, he says, "Clinicians are forced to prioritize therapies that will give the patient the greatest gains while lowering their CV risk."

Continued on next page ►

Illustration by Luisa Jung

UPDATED GUIDELINE FOR CCD

As research uncovers more effective ways to treat challenging and often coexisting conditions, the standard of care has evolved. To that end, the 2023 Multisociety Guideline for Chronic Coronary Disease, released by the American College of Cardiology (ACC), the American Heart Association (AHA) and others, has been updated to reflect recent findings in CCD treatment.[5] The revised guideline says that CCD (previously termed "stable ischemic heart disease") requires lifelong care by a multidisciplinary care team to forestall serious complications and preserve quality of life.[5]

Statins remain the first-line therapy for lipid control, with adjunctive treatments such as ezetimibe, inclisiran or PCSK9 inhibitors for patients who are at very high or high cardiovascular risk. Similarly, angiotensin receptor blockers, calcium channel blockers and thiazide diuretics continue to be first-line agents for controlling blood pressure.[5] Dr. Fonarow says a beta-blocker should also be considered for patients with hypertension and angina.

The new guideline contains several important updates that can help clinicians more effectively treat CCD in patients with diabetes. The following are some of the key takeaways:

Prescribe a SGLT2 inhibitor or GLP-1 RA

Originally developed to control AIC in diabetes, GLP-1 receptor agonists (GLP-1 RAs) and SGLT2 inhibitors have been shown in numerous studies to reduce the risk of CV events and CV-related deaths, as well as control blood glucose, in patients with diabetes.[5-6] Subsequent studies have shown the effectiveness of SGLT2 inhibitors in preventing hospitalizations in patients with heart failure as well as slowing the progression of chronic kidney disease, regardless of whether a patient has diabetes.[7]

The updated guideline recognizes the role newer classes of antihyperglycemics play in preventing acute CV events in patients with or without diabetes. Dr. Fonarow says these agents can help lessen the polypharmacy burden with their ability to prevent complications. "When I'm looking at coronary angiograms, patients with diabetes often have distinct changes that can stand out," says Raul J. Flores, MD, a cardiovascular disease specialist with the Atlantic Medical Group in Morristown, NJ. "Diabetes is such a calcifying illness. I'm supportive of any drug that offers a class cardiovascular benefit in these patients."

The revised guideline also provides recommendations for coronary intervention and revascularization to address severe ischemia or arterial blockage. "The foundational management of coronary disease with these newer agents, in combination with risk factor control and lifestyle modification, is as important or more important for keeping patients stable and preventing the need for invasive treatment later on," Dr. Fonarow says.

In addition to GLP-1 RAs and SGLT2 inhibitors, adjunct metformin may help prevent CV events in patients with CCD and diabetes, Drs. Fonarow and Flores suggest. While the CV data for metformin are not as robust as for GLP-1 RAs and SGLT2 inhibitors, researchers have found some potential benefits.[8]

Beta-blockers are not for all CCD patients

According to the new guideline, beta-blockers (once advocated for nearly all patients with CCD) are not recommended in patients with CCD who:

- have not had a myocardial infarction (MI) in the past year;
- have left-ventricular ejection fraction exceeding 50%;
- lack a primary indication for a beta-blocker.

However, either a beta-blocker or a calcium channel blocker is recommended as first-line antianginal therapy.[5] Thanks to advances in revascularization and antithrombotic and lipid-lowering therapies for patients after an MI, long-term (≥1 year) beta-blocker use is not recommended if left-ventricular systolic dysfunction is not present. Beta-blockers are still advised for CCD in patients with left-ventricular ejection fraction ≤40%.

Whereas the previous standard of care was to maintain lifelong beta-blocker therapy after an acute coronary syndrome regardless of heart failure presence, the updated guideline now advises clinicians to initiate beta-blocker therapy for 1 year after an MI, then revisit the prescription depending on clinical need.

Illustrations by Rocco Baviera

Both Drs. Fonarow and Flores agree that a patient's inability to tolerate a beta-blocker, usually due to fatigue, might dictate the need to stop the medication. "When I see patients with heart failure with preserved ejection fraction who are on beta-blockers, many are fatigued," Dr. Flores says. "Studies have shown that reducing beta-blocker use in select heart failure patients can help their exercise tolerance. When we are too aggressive with beta-blocker therapy, we can be exacerbating a sedentary lifestyle by creating exercise intolerance."

Encourage regular physical activity when not contraindicated[5]

The new guideline states that regular physical activity that increases lean body mass "may be more important to improving survival than achieving a normal body mass index,"[5] and reducing sedentary time is critical to decreasing hospitalizations and CV events by improving glycemic control, waist circumference and fat percentage.[5,9] The guideline recommends that patients with CCD who have no contraindications should:

- exercise 150 minutes/week doing moderate-intensity aerobic activity or 75 minutes/week of higher-intensity aerobic exercise;
- do resistance training exercises 2 or more days/week to improve

functional strength and cardiovascular risk control; and
- do lower-intensity activities (such as going for walks) to reduce "sitting time."[5]

"The heart is a muscle, but more than that the entire cardiovascular system is a muscle," Dr. Flores says. "Our arteries and our veins are like a pump—and if you don't use it, you lose it." However, getting patients who are sedentary to be active can be challenging. To help patients get started, advise them to:

- ***Ask about their everyday routine.*** Discuss what they could do differently, Dr. Flores advises. The guideline suggests simple changes to increase daily physical activity, such as taking the stairs instead of the elevator or doing more chores around the house instead of sitting.[5]
- ***Incorporate easy activities.*** Tell them to start with low-impact exercises, such as yoga or stretching. A program in which patients walk at a moderate pace for 10 minutes and then gradually increase speed and time is another option. "It can be intimidating to a patient who has been inactive, is fatigued and may have neuropathy, osteoarthritis or other issues to get up and go out for a jog," Dr. Flores says.
- ***Use smartphone apps for motivation.*** Fitness-tracking apps such as step counters and walking prompts can be conveniently downloaded to a smartphone and help keep your patients moving, Dr. Fonarow notes.

Referral to a cardiac rehabilitation program can also help patients increase and maintain their activity, Dr. Fonarow suggests. The new CCD guideline recommends this for all patients with CCD after a recent MI, percutaneous coronary intervention or coronary artery bypass graft; with stable angina or after a heart transplant; or after a recent coronary artery dissection event.[5] Patients exercise under supervision by trained therapists, learn heart-healthy lifestyle habits and interact with other patients with similar health challenges. For homebound patients, cardiac rehabilitation with remote instruction is another option.[10]

–by Pete Kelly

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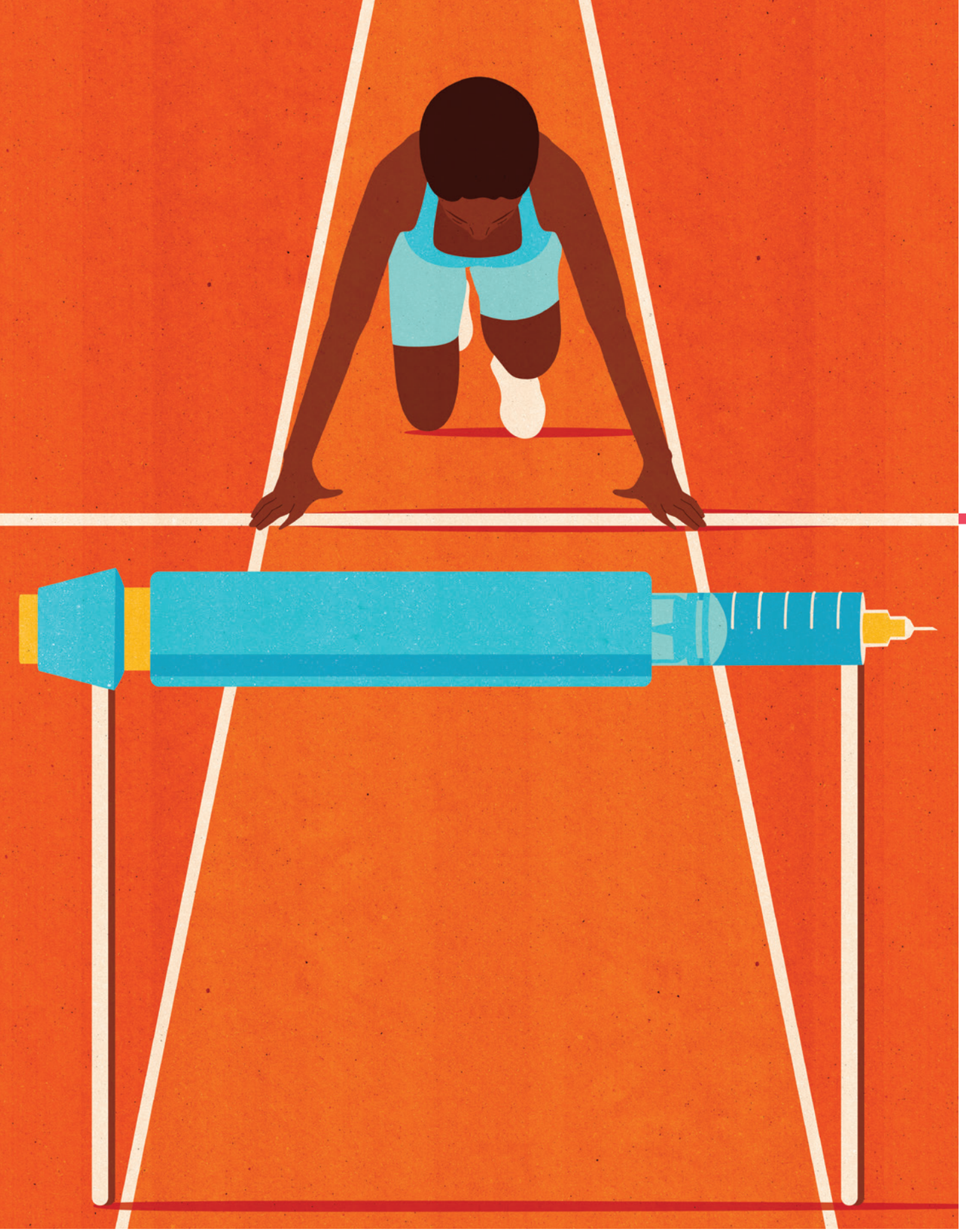

Illustration by Kotryna Zukauskaite

PRACTICE PEARLS

IMPROVING ADHERENCE TO **INSULIN THERAPY**

—BY ALEX EVANS, PHARMD, MBA

Certain barriers may keep patients from starting, or following, an insulin regimen. Here are ways to overcome such challenges to help ensure they stay on track with treatment.

Since its discovery in 1921, insulin has provided lifesaving treatment for millions of people suffering from diabetes—including the nearly 1 in 4 Americans with type 1 or type 2 diabetes who currently require insulin therapy.[1,2]

Studies have shown that adherence to insulin is crucial to ensuring positive outcomes. Patients who adhere to their insulin regimen enjoy better glycemic control and ultimately stay healthier. One study looking at claims data also found that patients with type 2 diabetes who were adherent to insulin had significantly lower total healthcare costs, despite having higher drug costs.[3]

Yet adherence to insulin remains a challenge. A 2022 review reported over half of type 2 diabetes patients on insulin had poor adherence, and only around 1 in 3 patients on basal insulin were adherent 3 years after beginning treatment.[4]

However, there is much you can do to improve the odds of long-term adherence. Here are strategies for working with patients to overcome challenges so they can get the most benefit from insulin therapy.

BARRIER:

Initiating insulin

One of the most common barriers to starting insulin is fear, especially in the beginning, notes Ji Hyun Chun, PA-C, MPAS, BC-ADM, a clinician at OC Diabetes & Endocrinology, Orange County, CA, and Past-President of the American Society of Endocrine Physician Assistants. While the reasons are varied, says Chun, they can include a fear of needles, a fear that needing insulin means they are getting sicker, fear of stigma and discrimination and fear that insulin use indicates end-stage disease. Patients feeling a sense of guilt or shame or even failure about the need to start insulin is also common.[5,6]

Finally, while patients with type 1 diabetes will always need insulin, some providers might feel unsure of when to start insulin in those with type 2 diabetes rather than a noninsulin glucose-lowering agent.

How to overcome it: When patients have fears about starting insulin, Chun says the key is to understand their concerns and address them directly. Sometimes, patients might have misconceptions about insulin the provider can clarify. For example, when type 2 diabetes patients feel that insulin means they are getting sicker, remind them that no medicine is necessarily lifelong. After possibly reversing some

NEWER OPTIONS MAKE INSULIN THERAPY EASIER

Advances in the formulation and delivery of insulin over the past decade give providers and their patients more choices than ever to find the right fit. These include:

- **Second-generation basal insulins with a longer duration of action,** often more than 24 hours, than their predecessors.[5] In addition, certain ones allow patients flexibility with timing if they miss a dose.
- **Insulin pens that make delivery easier and safer.** This includes the first FDA-approved smart insulin pen, which can help patients calculate the correct prandial dose, record information (e.g., time and date of administration) in a smartphone app and remind them when their next dose is due. This not only alleviates the burden of keeping a manual log but can also help patients better adhere to their regimen.[12]
- **Insulin pump systems with newer technology.** These wearable pumps can be integrated with continuous glucose monitoring to create a closed-loop insulin delivery system by using computer algorithms to adjust insulin delivery.[13]

beta-cell dysfunction, and with lifestyle intervention, some patients may be able to lower their dosage or wean off insulin. To ease injection fears, he recommends keeping demo pens and needles in the office to show patients and let them get comfortable using the insulin pen.

The decision to start insulin in patients with type 2 diabetes isn't necessarily straightforward, but in the 2022 clinical practice update from the American Association of Clinical Endocrinology (AACE), insulin is recommended for patients who have an A1C >10% or blood glucose >300, have significant signs of hyperglycemia or aren't able to reach their goals with noninsulin therapy.[7]

Chun echoes these recommendations. "I like to start insulin when a patient has symptomatic hyperglycemia or is not at goal despite optimizing noninsulin therapies. In patients who have asymptomatic severe hyperglycemia, I might use insulin to achieve better control before transitioning them to other therapies." He also finds insulin can be a good choice in situations where using a GLP-1 receptor agonist or SGLT2 inhibitor would be a concern due to the accompanying weight loss, such as in frail, older patients or those who are already underweight prior to initiating therapy.

BARRIER:

Cost

It's important not to overlook the financial challenges of taking insulin, especially considering its rising cost. More insulin options for patients also means more potential insurance formulary restrictions, including nonpreferred products or products not covered at all.

How to overcome it: Most manufacturers offer robust support programs, including copay cards, patient assistance and help with prior authorizations and tier exceptions to improve the chance your patients will be able to receive their prescribed therapy. Also, all major insulin manufacturers have committed to making insulin affordable, which includes price caps. This mirrors the $35 price cap enacted recently for all Medicare plans.[8] Also, it makes sense to enroll in a system to complete prior authorizations and tier exceptions electronically, like *CoverMyMeds.com*. Doing so will save your office time, allow pharmacies to send requests electronically and allow your office to track the status of each completed request.

TIP: Initiate the conversation with your patients by asking, "Are you having trouble paying for your medications?" Also, the Cost Conversations project has studied the issue and created clinician practice briefs with solutions,[9] available at *EssentialHospitals.org/cost-care/practice-briefs*.

BARRIER:

Fitting the regimen into the patient's lifestyle

Depending on the type of insulin, administration might require multiple injections per day as well as frequent blood glucose testing, a regimen many patients find difficult to adhere to over time. This can be especially problematic for students, frequent travelers and shift workers.

How to overcome it: With concerns about convenience, Chun notes that a good place to start is often a once-daily basal insulin. In this case, ultra-long-acting insulin can be a great option, and certain ones have a longer duration of action that allows it to be given at any time of day.

BARRIER:

Side effects

It's no secret that insulin can lead to weight gain and hypoglycemia, and the AACE guideline identifies both as top considerations when selecting pharmacotherapy. Such potential effects can also make many patients hesitant to start, or continue, on insulin. In addition, concerns about associations between insulin use and cardiovascular disease (CVD) are common among providers and patients.

How to overcome it: Weight gain is a challenge with insulin, but nutrition counseling and exercise can help, says Chun. Patients might also feel reassured knowing how much weight gain to expect. Patients with type 1 diabetes gained an average of about 4 lbs. after 1 year, and those with type 2 gained an average of 6.6 lbs. Chun wants patients to know that hyperglycemia may have led them to lose weight because their body was unable to properly use the calories in food. By improving glycemic control, they could gain back some of that weight. This is another opportunity to encourage lifestyle interventions that are at the core of diabetes management. Combining insulin with another agent that is associated with weight loss, such as an SGLT2 inhibitor or GLP-1 receptor agonist, may also mitigate weight gain.

The AACE recommends beginning with long-acting basal insulin analogs, and out of these, second-generation (ultra-long-acting) insulin is associated with less hypoglycemia than older types of insulin.[10] This can be an advantage for many patients, including those with a history of or at high risk for hypoglycemia and renal impairment.

While studies show those with type 2 diabetes who require insulin have a higher risk of CV events, clinical trials for newer types of basal insulin failed to find an association.[11] Patients should know that CV risks of uncontrolled hyperglycemia are higher than any potential risks of insulin use. ●

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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%	**-1.3%**	**-0.8%**
p<0.001 vs Januvia® (Baseline: 8.4%)	*p*<0.001 vs Januvia® (Baseline: 8.3%)	(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	**-6.8 lb**	**-1.3 lb**
ETD: -3.5 lb (95% CI: -4.4, -2.4) vs Januvia® (Baseline: 201 lb)	ETD: -5.5 lb (95% CI: -6.6, -4.4) vs Januvia® (Baseline: 201 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%	**-0.9%**
p<0.001 vs Jardiance® (Baseline: 8.1%)	(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	**-8.1 lb**
ETD: -0.2 lb (95% CI: -1.5, 1.1) vs Jardiance® (Baseline: 202 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.

For information about RYBELSUS® contact:
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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

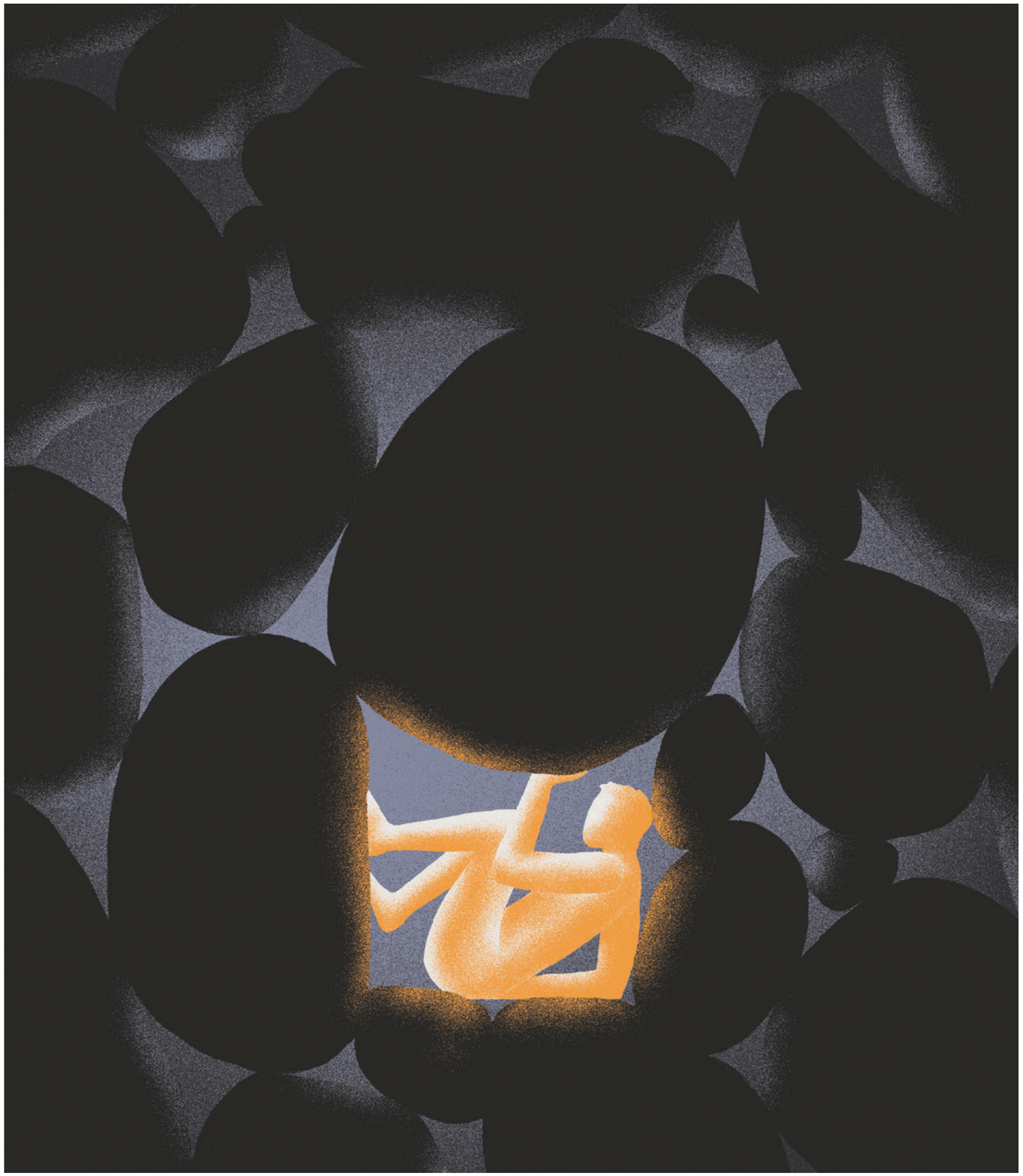

Illustration by Matt Chinworth

PATIENT ENGAGEMENT

Addressing depression in patients with diabetes

For many, trying to manage diabetes is like a full-time job—one that comes with mental challenges that often go untreated. Here, experts offer ways to help patients cope with their depression.

Patients with diabetes are 2 to 3 times more likely to suffer from depression than those without the disease, according to the Centers for Disease Control.[1] Equally troubling is that only 25% to 50% of those patients get diagnosed and treated for depression.[1,2] "The numbers are outrageous," says Betul Hatipoglu, MD, Director of the Diabetes and Metabolic Care Center at UH Cleveland Medical Center. "Managing depression begins with recognizing it, and we need to be aware of the symptoms—some of which can be easily missed—especially when our clinical practices get busier."

Research also 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 the management of their disease.[3] While there are similar symptoms, diabetes distress differs from clinical depression.[4] "Diabetes distress looks a lot like depression, but it can't be treated as effectively with medication due to poor adherence," Dr. Hatipoglu says. "Many of my patients tell me they feel discouraged, worried and are tired of dealing with daily diabetes care. They say diabetes is like a full-time job with no vacation days."

Experts believe that people with diabetes are at an increased risk for depression due to the chronic nature of the disease and the stress involved with managing it. "The constant need for self-management

tasks, such as medication adherence, monitoring blood glucose levels, adhering to a specific diet and engaging in regular physical activity can be overwhelming and lead to feelings of frustration and burnout," says Joanna Mitri, MD, Research Associate at the Joslin Diabetes Center in Boston, and Instructor at Harvard Medical School. And when you add the fear of disease progression, developing complications and the impact of diabetes on daily life, you have a recipe for depression. "For people who have depression, an unhealthy lifestyle that includes a poor diet, lack of exercise and disordered sleep may also increase the risk of developing diabetes," Dr. Mitri says. "These behaviors can activate the stress system." Here are ways to recognize signs of depression and make sure patients receive the proper treatment.

Screen often—and encourage patients to open up.

"I use a holistic approach to screening for depression in my patients by integrating both informal and formal methods into my practice," explains Dr. Mitri. "I make it a point to inquire about various aspects of my patient's life, including home and work situations. I try to pay attention to changes in their behavior, mood and overall demeanor during visits." She says that HCPs need to create a safe and supportive environment that will encourage patients to be open about their experiences and feelings.

In addition to annual screenings and intake questionnaires, Dr. Mitri performs more frequent assessments for those who self-report depressive symptoms. "A positive screening requires further evaluation to confirm a diagnosis and to determine the most appropriate course of action for each patient." The latest AACE guidelines stress the need for increased awareness of psychosocial factors in diabetes care.[5] Common signs of depression to watch for:[2]

- Feeling sad or empty.
- Losing interest in favorite activities.
- Overeating or not wanting to eat at all.
- Not being able to sleep or sleeping too much.
- Having trouble concentrating or making decisions.
- Withdrawing from friends and family.
- Feeling hopeless, irritable, anxious or guilty.
- Having aches and pains, headaches, cramps or digestive problems.
- Having thoughts of suicide or death.

Add mental health providers to the team.

When treating diabetes, HCPs often take a team approach that includes endocrinologists, educators and ophthalmologists—but not a mental health professional. "One team member we must also consider is a mental health provider," Dr. Hatipoglu says. "This could be a psychologist, psychiatrist or both in many cases. We need the support of a psychotherapist because pharmacotherapy alone does not necessarily solve the long-term effect of depression if the patient doesn't receive tools to manage the condition. We often miss this fundamental intervention that might provide prevention."

Validate their feelings.

Dr. Hatipoglu says listening to patients is the best way to spot red flags for depression or distress. "I listen to my patients and show them that I understand their perceived emotional burden or diabetes distress," she says. "I also let them know they're not alone, and that their sadness or frustration is not a sign of weakness or failure." Dr. Hatipoglu also stresses the importance of early treatment for mental health, which might include antidepressants. "I explain that some medications we use to treat depression are like a replacement for missing chemicals in their brain. I compare it to vitamin D deficiency."

> "Let them know they're not alone, and that their sadness or frustration is not a sign of weakness or failure."
>
> *—Betul Hatipoglu, MD*

Encourage self-care.

Both Dr. Hatipoglu and Dr. Mitri agree that educating patients with diabetes about self-care, healthy lifestyle behaviors and coping techniques for depression can have an enormous impact. According to a recent systematic review and meta-analysis, the most compelling evidence linking nutrition to mental health was found for the Mediterranean diet and incident depression.[6] "We always start with nutrition," Dr. Hatipoglu says. "There are clear benefits in the Mediterranean-style diet for patients with diabetes who are suffering from depression."

In addition to a healthy diet, physical activity can help ease symptoms of depression or anxiety and keep them from returning once patients are feeling better. Regular exercise helps reduce stress and improve mood by:

- ***Releasing feel-good endorphins,*** the natural brain chemicals that can improve a sense of well-being.
- ***Refocusing negative thoughts.*** Focusing on a physical activity instead of worrying can get patients out of the cycle of negative thoughts that feed depression and anxiety.
- ***Increasing confidence.*** Meeting exercise goals or challenges, even small ones, can boost self-confidence.
- ***Encouraging social interaction.*** Exercise and social activity, be it group activities, walking the dog or taking a walk around the neighborhood, may give patients the chance to meet or socialize with others.

Illustration by Jesse Zhang / Ikon Images

Self-care interventions such as guided meditation, soothing sounds like waves and relaxation apps can also help patients calm their negative thoughts. "Bright light therapy, also called phototherapy, and music therapy are included in the multiple practice guidelines as treatments for depression," Dr. Hatipoglu notes.[7]

Screening patients for depression should be a regular part of any diabetes treatment plan. "By addressing depression alongside diabetes management, HCPs can minimize the risk of exacerbating diabetes complications and enhance overall patient well-being," Dr. Mitri says.

—by David Levine

> "Pay attention to changes in their behavior, mood and overall demeanor during visits."
>
> *—Joanna Mitri, MD*

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PATIENT: RACHEL, 69, WAS DIAGNOSED WITH TYPE 2 DIABETES IN 2016. SHE HAD SEVERAL RELATED COMPLICATIONS, INCLUDING HYPERTENSION, HYPERLIPIDEMIA AND OBESITY.

"Her main goals were to improve her glycemic control and lower her CV risk"

PHYSICIAN:

Stephen Brunton, MD, FAAFP, CDCES

Director, US Primary Care Metabolic Group, Winnsboro, SC

History:
When Rachel came to see me for her annual physical her A1C was 8.3%, the highest it had ever been. Rachel's A1C had fluctuated over the years. At the time, she was taking a combination metformin/DPP-4 inhibitor. She was also taking valsartan for hypertension and rosuvastatin for hyperlipidemia. In addition, Rachel weighed 143 lbs. with a BMI of 30. She also had a family history of obesity and cardiovascular disease (CVD).

Rachel, who was married and had grandchildren, enjoyed cooking for her family at home. She tried to make healthy meals, and if she did cook a family favorite such as pot roast and gravy, she ate a smaller portion. She walked her small dog daily for 20 minutes but was otherwise sedentary. Her main treatment goals were to improve her glycemic control and lower her cardiovascular risk.

Initiating treatment:
I recommended she start a GLP-1 receptor agonist (GLP-1 RA), which could help lower her A1C and lose weight. In addition, I told her certain GLP-1 RAs are indicated to lower the risk of CV events. We discussed the possibility of nausea and other gastrointestinal side effects that are common when starting a GLP-1 RA or increasing the dose. To avoid this, I advised her to eat low-fat food and smaller meals. Specifically, I told her to eat half her meal and wait 20 minutes, and if she was still hungry, eat half of the remaining meal and wait another 20 minutes. If she was still hungry after that—finish the meal. I instructed her to take the GLP-1 RA first thing in the morning on an empty stomach with 4 oz. of water and to wait 30 minutes before eating or taking other medications.

I told Rachel that, although it was good that she walked her dog, she also needed to incorporate regular moderate-intensity exercise (at least 5 days a week for at least 30 minutes each time) to achieve the cardio benefits that would aid weight loss and lower her CVD risk. For the same reasons, I also suggested she follow a Mediterranean diet or at least increase her vegetable intake.

After 3 months, Rachel had lost 7 lbs. and her A1C dropped to 7.3%. She had nausea when starting her medication, but it had dissipated within a week. In addition, Rachel was cooking and eating more fish and less red meat. She had also bought a bicycle, which she rode 3 to 5 days a week, including with her grandkids, who were impressed that she could keep up with them!

Considerations:
For patients like Rachel, GLP-1 RAs offer many benefits, including improved glycemic control, weight loss and low risk of hypoglycemia. Certain agents also have cardiovascular and renal benefits as confirmed in major outcomes trials. In addition, Rachel's case shows that it's important to define "exercise" for patients—that is, they need to do a physical activity that is intense enough for long enough (if safe to do so) versus "taking a stroll" to maximize the CV and weight-loss benefits of regular exercise.

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

PATIENT: CALVIN, 69, WAS DIAGNOSED WITH TYPE 2 DIABETES 14 YEARS AGO. HE ALSO HAD CORONARY ARTERY DISEASE, HYPERTENSION, HYPERLIPIDEMIA AND CHRONIC KIDNEY DISEASE.

"He was not aware of the relationship between his kidneys and his heart"

CLINICIAN:

Lucia M. Novak, MSN, ANP-BC, BC-ADM

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

History:
Calvin came to me 3 months ago after relocating from another state. He weighed 184 lbs.; his BMI was 27.2 and his BP was 134/78. Calvin's A1C was 6.4% and his urine albumin-to-creatinine ratio (UACR) remained above 300 mg/g creatinine for more than a year. He had coronary bypass surgery 10 years ago. Calvin was on a weekly GLP-1 receptor agonist (GLP-1 RA). He said he could not tolerate metformin.

He walked his dogs 3 times daily for at least 40 minutes. He also had lost weight, so he no longer had pain in his knees. He told me his wife did all the cooking—"nothing fried"—and said, "I think I am turning into a chicken I eat so much of it!" Calvin understood that his heart disease placed him at higher risk for both a heart attack and heart failure. He said his goal was to protect his heart as much as possible, but he was not aware of the relationship between his kidneys and his heart.

Initiating treatment:
We discussed renal disease and I explained that it can remain asymptomatic even when significant damage exists. I added that kidney health directly impacts heart health, and vice versa. Even though his A1C was at goal, I said adding another diabetes medication would provide additional protection to both his heart and kidneys. I suggested that he go on an SGLT2 inhibitor, which would significantly reduce his risk of being hospitalized for heart failure and improve the health of his kidneys.

We started Calvin on the lowest once-daily dose. I also counseled him on common side effects of SGLT2 inhibitors, including dehydration and genital mycotic infections. Specifically, I reviewed proper perineal hygiene and signs/symptoms of urinary tract and genital infections. I also instructed him to drink more water to prevent dehydration—especially when paired with a GLP-1 RA, which reduces appetite as well as feelings of thirst.

> "Calvin understood that his heart disease put him at higher risk for both a heart attack and heart failure."

At his 3-month follow-up, he had lost 2 lbs., his BMI was down to 26.9, his blood pressure and A1C were excellent and his UACR was below 300 mg/g creatine. At Calvin's most recent visit, his UACR was 280 mg/g creatinine—an improvement from his previous result of 324 mg/g creatinine. I explained that this number should continue to improve with time, and we will continue to monitor his renal status every 3 months. He is pleased that his kidneys are getting better, he feels well and has no complaints.

Considerations:
Renal disease can continue to progress despite optimal medical management and attainment of treatment goals. This case illustrates the importance of utilizing pharmacotherapies such as SGLT2 inhibitors that have direct renal benefit and reduction of risk, regardless of baseline A1C and other medication being used. It's also important that patients fully understand their overall health and how their comorbid conditions impact each other. The optimal management of cardiorenal disease will typically require multiple medications. Patients tend to be more willing to take and continue with these critical therapies if they understand the rationale for their use.

Illustrations by Juhee Kim

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Expert insight on diabetes management

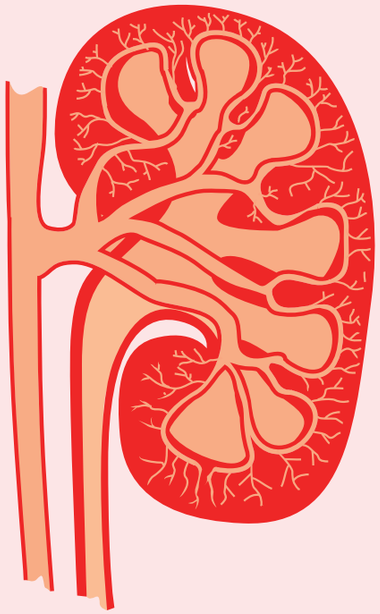

Illustration by vektorjunkie / Getty Images

Guarding against renal disease

Q: What are important considerations when managing diabetic kidney disease (DKD) in patients with type 2 diabetes?

A: Type 2 diabetes is a leading cause of renal failure. The most important aspect of managing DKD is making the diagnosis. Many physicians are under the impression that the presence of albuminuria is necessary but that's not the case. Diagnosis of DKD is based on the presence of albuminuria and/or decreased eGFR (45 to 59) on two or more occasions. It's best to confirm the diagnosis using a cystatin-C calculation. Once the diagnosis is made, there is an extremely high risk for increased mortality (4-fold greater with albuminuria, 6-fold greater with low eGFR and 10-fold greater when both are present). Excess mortality is primarily due to cardiovascular disease (CVD), but also due to heart failure and progression of renal failure. These patients should be treated as having CVD equivalents and have maximal treatment for the prevention of myocardial infarction, heart failure and end-stage renal disease. This should include prescribing RAAS inhibitors, statins, antiplatelet agents, SGLT2 inhibitors and, if needed, GLP-1 receptor agonists.

–Carol H. Wysham, MD, *Clinical Professor of Medicine, University of Washington; endocrinologist at Rockwood Clinic in Spokane*

Glucose monitoring

Q: When do you recommend continuous glucose monitoring (CGM) to a patient?

A: I would recommend the use of continuous glucose monitoring to most people with type 1 diabetes and research is showing that it might help those with type 2 diabetes as well. It is particularly helpful for those on intensive insulin therapy, those who have hypoglycemic unawareness (a condition when people lose their natural defenses to sense low glucose/sugar levels) and for patients with high and low glucose patterns in general. CGM devices work through a sensor placed on the skin. It transmits readings to a small recording device. Whether patients manage their diabetes with a pump, daily injections or oral medications, CGM can help them better manage their blood glucose.

–Robert Gabbay, MD, *PhD, Chief Scientist and Medical Officer, American Diabetes Association*

Addressing obesity

Q: Why is it important to take an integrative approach when treating patients with diabetes who have obesity?

A: Diabetes patients who are living with obesity or overweight often have been managing weight problems and stigma for many years, frequently starting as a child or teenager. I share with my patients the concept that obesity is a disease, just like diabetes, and our goal with weight loss is to help improve their diabetes and reduce the risk of complications, including high cholesterol, high blood pressure and heart disease. People often find it daunting when they consider how much weight they feel they need to lose (e.g., 50 lbs. or 100 lbs.), which seems insurmountable. I educate my patients that our goal is to help improve their quality of life, and losing as little as 5% of their body weight can result in health benefits.

In addition, there can be coexisting depression or stressors at home, and it's important to acknowledge and treat any underlying mood issues to help patients with their psychosocial well-being. Importantly, I look at their current medications and ensure they are weight-favorable or weight-neutral. If it's possible to switch medications associated with weight gain with a weight-neutral option, I consider this as well in conjunction with their PCP. There are many factors to consider as part of a holistic approach to weight loss to help patients on their journey to a healthier body weight.

–Rachel Pessah-Pollack, MD, FACE, *Clinical Associate Professor of Endocrinology, Diabetes and Metabolism, NYU Langone Health*

Tailoring A1C goals to the patient

Q: What factors do you consider when setting a patient's A1C goals?

A: There are general goals set by the AACE and ADA, but it's also important to individualize such targets based on the patient's characteristics and other factors. For example, people with newly diagnosed diabetes and those with longer life expectancy may benefit from more stringent efforts to lower their AlC. In those instances, I think it's beneficial to treat aggressively to reach these goals, if it can be done safely.

However, we need to be careful in preventing hypoglycemia and other side effects related to escalating therapy. I believe once the decision is made with this in mind, there should be a clear plan of treatment to achieve the agreed upon goal. When patients are motivated to keep their goal, I would recommend spending time explaining how to manage side effects and ways to minimize risks rather than de-intensifying therapy. On the other hand, patients with severe complications or comorbidities, the A1C goal could be less stringent. Regardless of age or comorbidities, any treatment decision should consider the patient's preference and the available resources and support.

–Joanna Mitri, MD, *Research Associate, Joslin Diabetes Center, Boston; Instructor in Medicine, Harvard Medical School*

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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*.