Individualized Management of Patients with T2DM and Comorbidities While Reducing Hypoglycemia Risk

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Contents:

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ACTIVITY OVERVIEW

Hypoglycemia remains the rate-limiting factor in the achievement of glycemic goals in patients with type 2 diabetes mellitus (T2DM) treated with pharmacotherapy. Unfortunately, hypoglycemia is common among patients with type 1 and type 2 diabetes mellitus and can have serious clinical consequences when not managed properly. According to national surveillance data, annual rates of severe hypoglycemic events are likely grossly underestimated, with self-reported severe events occurring in approximately 12% of patients annually. Given the potentially dangerous consequences of hypoglycemia, PAs must remain up to date on all aspects of T2DM management, especially in those with significant comorbid conditions.

AAPA TAKES RESPONSIBILITY FOR THE CONTENT, QUALITY, AND SCIENTIFIC INTEGRITY OF THIS CME ACTIVITY.

EDUCATIONAL OBJECTIVES

At the conclusion of this activity, the PA should be better able to:

- Identify risk factors and comorbid conditions that may increase the risk of hypoglycemia.
- Choose individualized A1C treatment goals accordingly.
- Select newer treatment options with a low risk of hypoglycemia.
- Use therapies that demonstrate cardiovascular and renal benefit in patients at heightened risk.

ACCREDITATION STATEMENT

This activity has been reviewed by the AAPA Review Panel and is compliant with AAPA CME Criteria. The activity is designated for 1.5 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation. Approval is valid through November 30, 2021.

Estimated time to complete this activity: 90 minutes.

HOW TO RECEIVE CREDIT

There are no fees for participating and receiving CME credit for this activity. Participants must: 1) read the educational objectives and faculty disclosures; 2) study the educational materials; 3) complete the post assessments in Learning Central.

In order to receive credit, participants must complete the post-test and evaluation. You will be able to access your certificate of completion in Learning Central as soon as you complete the post-test with a minimum score of 70%. Your certificate will be available under "Transcript" for your records.

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All individuals in a position to control the content of this activity have disclosed their relevant financial relationships with commercial interests. Disclosures from the author(s) are listed below.

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eCASE CHALLENGE #1

Lawrence Herman, DMSc, MPA, PA-C, DFAAPA: Hello, and welcome to this video *eCase Challenge*, "Individualized Management of Patients with Type 2 Diabetes and Comorbidities: Reducing Hypoglycemia Risk." I'm Lawrence Herman, President of Palantir Healthcare LLC in Boiling Springs, South Carolina, and a Past President of the American Academy of PAs in Alexandria, Virginia.

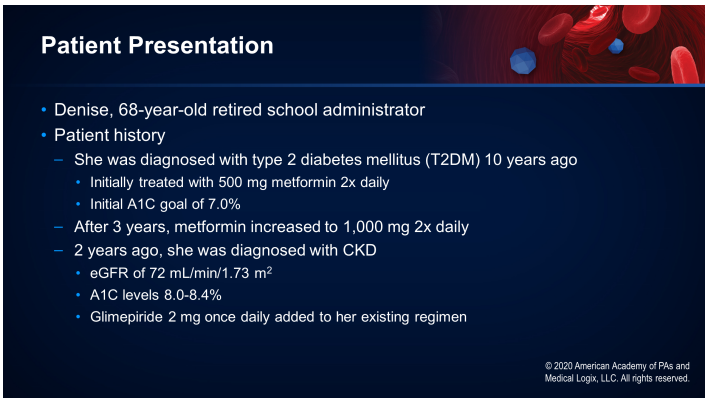
Joining me today is PA Melissa Murfin, Associate Professor and Research Coordinator in the Department of Physician Assistant Studies at Elon University in North Carolina. My thanks to you for your involvement in this important continuing medical education activity, which consists of two video *eCase Challenges*.

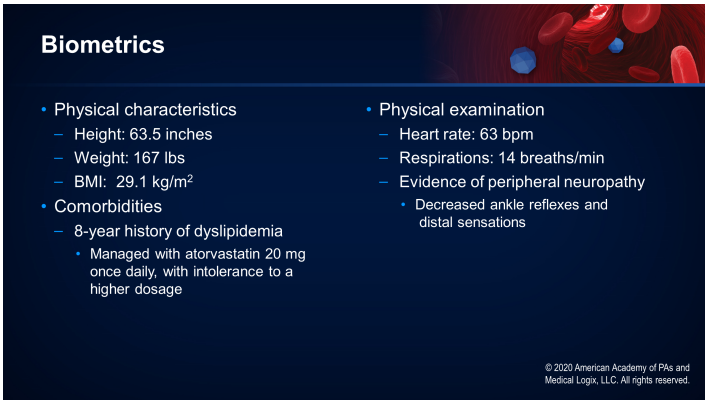
So let's get started with our first case. Our case challenge is a patient we will call Denise. Denise is a 68-year-old retired school administrator who is in the office for her 3-month checkup. She was diagnosed with type 2 diabetes mellitus 10 years ago, which was initially treated with 500 mg metformin twice daily.

Her primary care provider set an initial A1C goal of 7.0%. With diet and exercise, she was able to control her A1C for 3 years before metformin was increased to 1,000 mg twice daily.

With the death of her husband 2 years ago, Denise's health took a downward turn. She was diagnosed with stage 2 chronic kidney disease, with an estimated glomerular filtration rate of 72, and began to have trouble managing her A1C levels consistently.

At her regular office visits, her A1C levels frequently fluctuated between 8.0 and 8.4%. Based on Denise's desire to remain on oral therapy, her primary care provider added sulfonylurea, glimepiride 2 mg once daily.

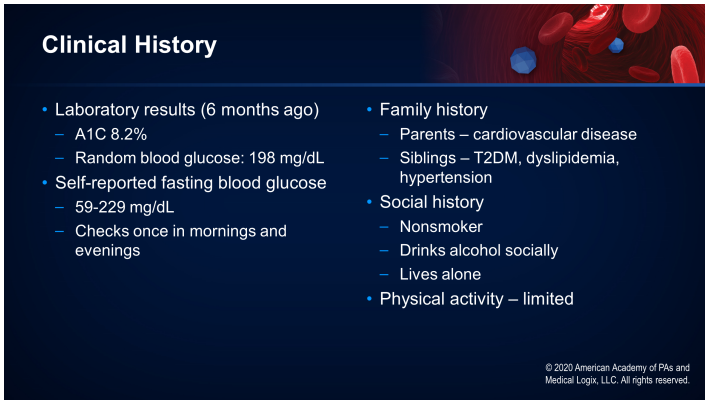




Denise's medical chart reveals that she is considered overweight based on her BMI. She has an 8-year history of dyslipidemia, which is managed with a statin. On physical exam, her heart rate and respiration are normal. She has some evidence of peripheral neuropathy based on decreased ankle reflexes and decreased distal sensations.

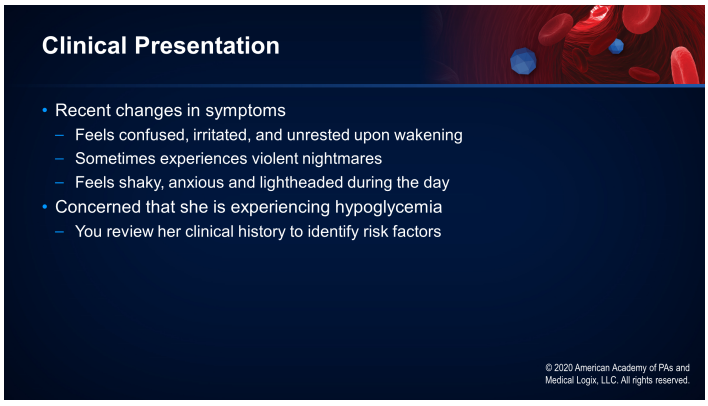
Laboratory results from 6 months ago show an A1C of 8.2% and a random blood glucose level of 198 mg/dl. She reports her fasting blood glucose levels range from 59 to 229 mg/dl. When you ask about self-monitoring of blood glucose levels, Denise admits to checking typically once in the mornings and the evenings.

Denise's family history shows that both parents had a history of cardiovascular disease, and her father also had type 2 diabetes. Her two sisters also have a history of type 2 diabetes, dyslipidemia, and hypertension. Her social history shows that she is a nonsmoker, drinks alcohol occasionally and currently lives alone. Her regular physical activity is limited.



During the visit, you ask Denise if she has experienced any recent changes in symptoms. She states that in the last few months, she has sometimes woken up from sleep in the mornings feeling confused, irritated, and generally doesn't feel rested. She also sometimes has violent nightmares and reports feeling shaky, anxious, and lightheaded during the day.

You are concerned that Denise might be experiencing some symptoms of hypoglycemia. You review Denise's clinical history again to identify potential risk factors, which are an important aspect of care and can direct therapeutic decision-making.



Now, let's pose our first clinical question.

Question 1

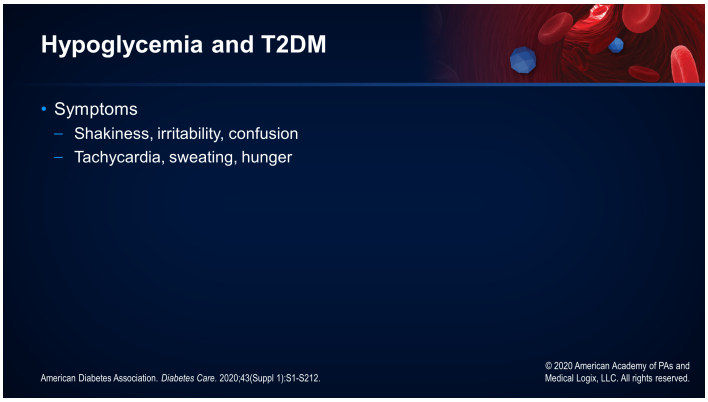
Which of the following factors is associated with an increased risk of hypoglycemia?

A. Age less than 50 years
B. Chronic kidney disease
C. Hypertension
D. Short duration of diabetes

Melissa, thanks for joining us for this important discussion.

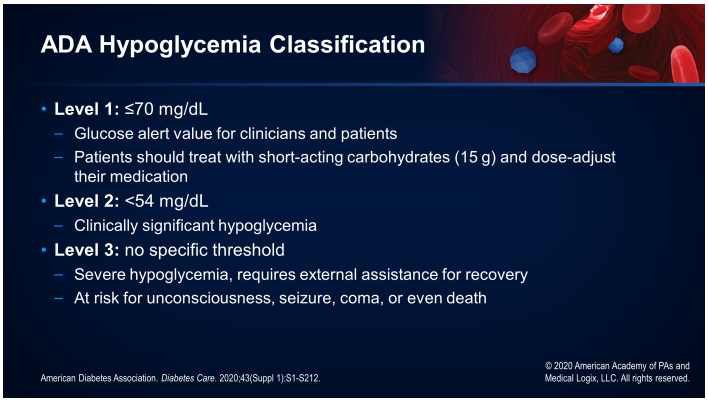
Let's begin by talking about hypoglycemia and what the major limiting factors are in patients achieving their glycemic controls in type 2 diabetes. And of course, prevention of downstream sequelae associated with diabetes is a critical part of management.

One of the things that are very commonly seen in patients who may not necessarily be managed correctly, but even in those who are, is hypoglycemia symptoms, which include things like shakiness, irritability. People can be confused. They get tachycardic, sweaty. They can get some hunger pangs.



Now, the ADA classifies hypoglycemia in various levels, level 1, 2 and 3. And level 1, which is the lowest, is folks who typically have a glucose alert value of 70 mg/dl or lower, and they can typically be treated with a fast-acting carbohydrate, 15 g orally, and dose adjustment of their glucose-lowering therapy subsequently.

They can also have more significant hypoglycemia, level 2, which is less than 54 mg/dl. And that's a pretty serious and clinically important level of hypoglycemia.



The third level of hypoglycemia is severe. It's no specific level, but it's associated with severe cognitive impairment, and it requires some third-party or external assistance for the patient to recover. Without that, it can progress to things like loss of consciousness, potentially even a seizure or coma and, unfortunately, death.

There are a lot of things associated with that level of hypoglycemia and the risk of hypoglycemia. Can you walk us through a few of those and clarify why people may get hypoglycemic?

Melissa Murfin, PA-C, PharmD, BCACP: Absolutely, Larry. Thank you. As you know, and we are learning more and more about the impact of hypoglycemia on our diabetes patients, we recognize that numerous risks for the patients themselves actually will play into elevating their risk of hypoglycemia during treatment.

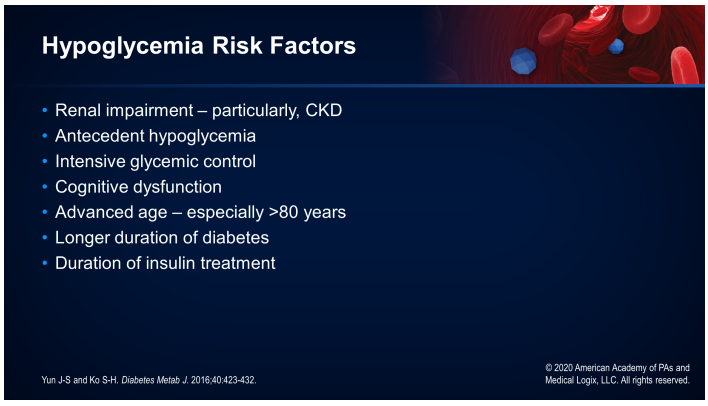
Patients that have renal impairment, particularly those with chronic kidney disease, may be more likely to experience hypoglycemic episodes. The reason for this is part of our physiology. The kidneys play a very important role in metabolizing insulin, in production of glucose or gluconeogenesis and reabsorbing glucose, and also a huge role in excreting drugs and their metabolites.

We also notice that patients who have antecedent hypoglycemia are at greater risk. One event or one precipitating hypoglycemic occurrence can actually cause now a vicious cycle of continued recurrent events. And part of that is that their counterregulatory process has now become defective over time.

One thing, as practitioners, that we can actually impact is glycemic control. A lot of goals have changed in terms of what the Diabetes Association recommends for patients as far as whether or not we need intensive glycemic control.

Additional risk factors that we see in our patients for hypoglycemia include cognitive dysfunction, which we see in our patients with type 2 diabetes, who have higher rates of dementia, and vice versa. Severe dysfunction is associated with approximately a twofold increased risk of severe hypoglycemic events.

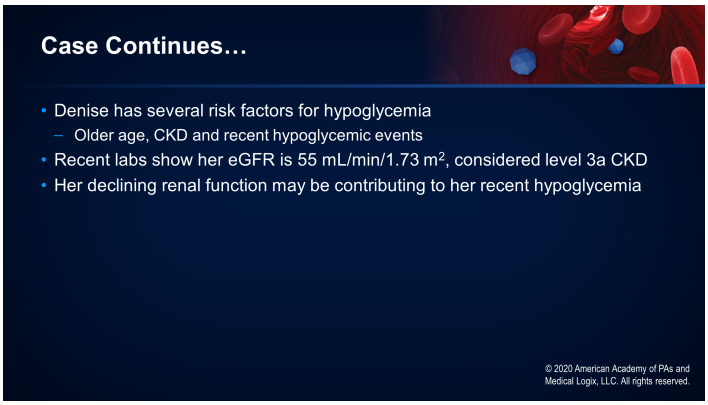
We're also concerned about our patients with advanced age. So particularly those elderly folks or our very elderly patients who are over 80 years of age, as that may increase their risk of hypoglycemia, worrying about the potential for a fall, which could cause greater complications and comorbidities, in particular, in that age group.



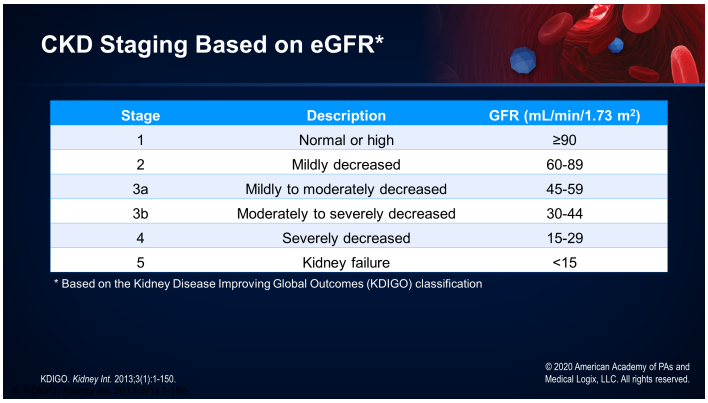
Our folks that have had diabetes for longer durations also have an increased risk of hypoglycemia. And the folks, in particular, that are using insulin and the length of time that they've been treated with insulin -- longer duration of insulin use increases their risk of hypoglycemic events.

Let's review the question posed, which asked, which of the following factors is associated with an increased risk of hypoglycemia? The correct answer is (B), chronic kidney disease.

Looking at Denise's clinical history, you note that that she has many of these risk factors for hypoglycemia, including older age, chronic kidney disease and what appears to be recent hypoglycemic events. Labs drawn just prior to the visit indicate that her EGFR is now 55 mm/min/1.73 m^2, indicating that her kidney function has diminished further to stage 3a chronic kidney disease. This declining renal function may be contributing to her recent hypoglycemia.



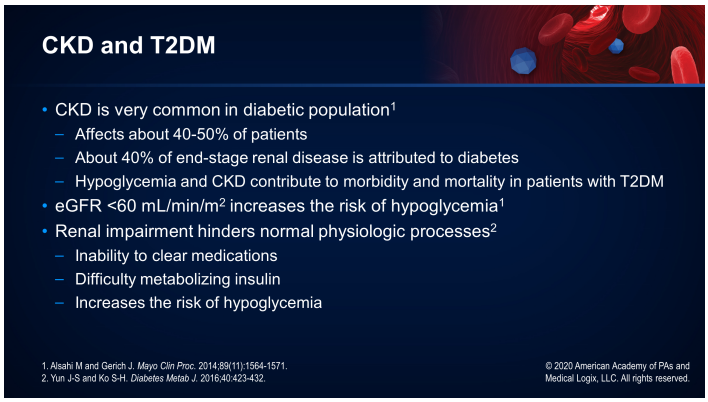
Let's take a few moments to review the stages of chronic kidney disease, which are based on EGFR rates. It is important to review these values because therapies can be recommended or contraindicated based on the stage of disease.



Lawrence Herman: This is very prevalent among patients with both type 1 and type 2 diabetes. Roughly speaking, about what percentage of patients are impacted in this population?

Melissa Murfin: So the percentage of patients that is affected is about 50%. Kidney disease is very prevalent amongst our diabetes patients in both type 1 and type 2 diabetes. About 40% of end-stage renal disease is actually attributed to diabetes. And when we put hypoglycemia and chronic kidney disease together, they're both significant causes of morbidity and mortality in our diabetes patients and in that population.

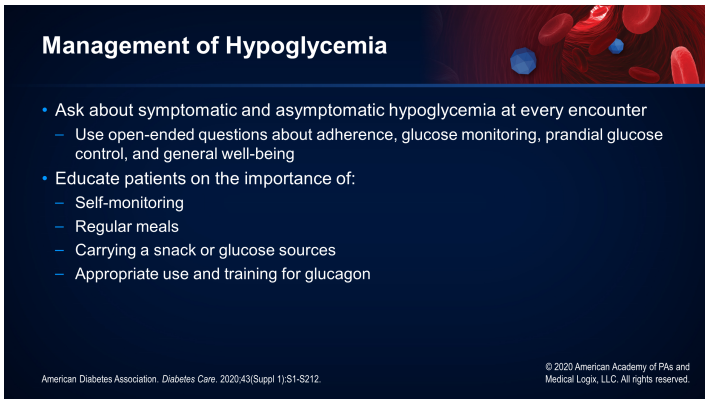
The risk of hypoglycemia is also going to increase significantly as the GFR lowers. So, when EGFR is less than the 60 ml/min/1.73 m^2, we see an increased risk of those hypoglycemic episodes. This often has to do with the kidney's role in physiologic processes.



Renal impairment's going to hinder these processes, and we'll see a lot of patients have an inability to clear those medications effectively and also have some more difficulties metabolizing insulin, which predisposes the patient with chronic kidney disease to hypoglycemia.

The American Diabetes Association recommends that clinicians ask about both symptomatic and asymptomatic hypoglycemia at every encounter. One way to do this is through the use of open-ended questions to determine the patient's adherence to therapies, glucose monitoring, prandial glucose control, and general well-being of the patient.

You should continue to educate patients on the importance of self-monitoring, regular meals, and carrying a snack or glucose sources in the case of a hypoglycemic event. The appropriate use of glucagon should be discussed and training given in the event it is needed.



Before we present more of Denise's case, we have a new clinical question.

Question 2

Of the following choices, what is the best approach with Denise to address her hypoglycemia?

A. Add NPH insulin to her current regimen to reduce her A1C further.
B. Increase self-monitoring of blood glucose.
C. Stress a more strict regimen of diet and exercise.
D. Use continuous glucose monitoring to capture her blood glucose profile.

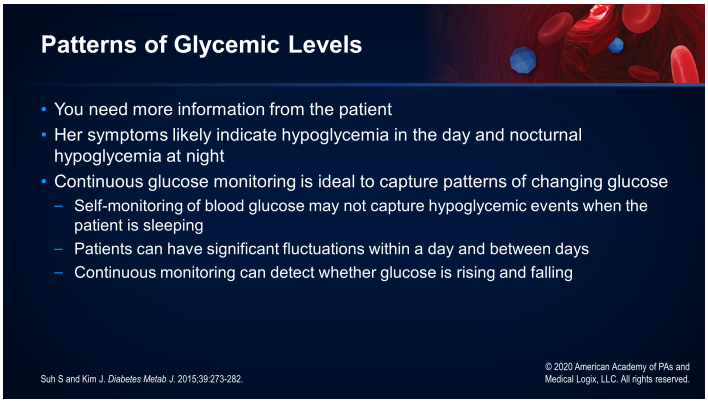
Lawrence Herman: Now, we need more information from Denise on the pattern of her glycemic levels, and her symptoms very likely indicate that she's experiencing hypoglycemia both in

the day and having nocturnal hypoglycemia while she's asleep, which has a much more ominous potential for any patient.

Ideally, continuous glucose monitoring would be what we would want to have. Sometimes it is difficult to get that approved in primary care, depending upon the patients' insurance.

A patient can, as an alternative, increase their self-monitoring blood glucose testing and may be able to capture hypoglycemic events, but not likely when they're asleep unless they wake up and test at that moment.

Patients can have very significant fluctuations within a day, and between different days of the week, depending upon things like weekday, weekend activities, exercise, their meals. A wide variety of things can impact that. So ideally, continuous glucose monitoring would be able to detect whether the patient's blood glucose is rising or falling and what the pattern would be on a day-to-day basis. So, beneficial for several reasons, especially since type 2 diabetes is progressive in nature, and most patients will need to escalate medications and eventually need insulins.



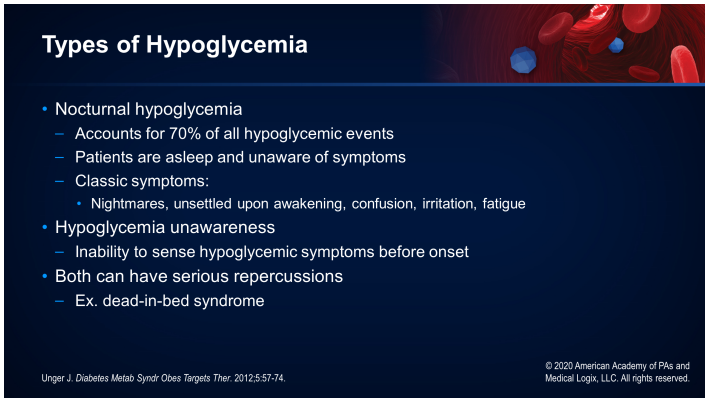
So, the concern is nocturnal hypoglycemia as I look at this. Are you equally concerned about that?

Melissa Murfin: Absolutely. We know that nocturnal hypoglycemia accounts for about 70% of all hypoglycemic events, and one of the concerns is that the patients are asleep and they're unaware of the symptoms. So, they may not be perceiving those nighttime lows that could be very significant for them.

Classically, what patients may tell you about include those nightmares during sleep, and they may feel rather out of sorts when they wake up. Patients may describe confusion, irritation, and fatigue as if they haven't slept at all during the night. So those episodes and being able to capture them are very important for treatment for the patient.

Another concern for Denise is that she may also be experiencing some hypoglycemia unawareness, which is that inability to sense those hypoglycemic symptoms. So, the patient may actually not be aware that they are having those depressions in their blood glucose levels. They won't be able to perceive those symptoms at all.

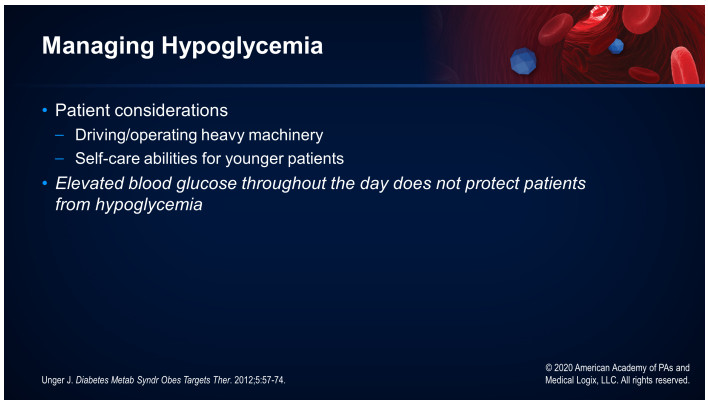
There can be some very serious repercussions for these hypoglycemia unawareness and nocturnal hypoglycemia. There's a term, dead-in-bed syndrome, which discusses things like other arrhythmias that may lead to sudden death for a patient who's experiencing hypoglycemia and is unaware of those symptoms. So, there are a lot of concerns for patients and for their caregivers when the patient's experiencing these severe hypoglycemic events and doesn't perceive those symptoms at all.



Denise, in particular, has large variability in her blood glucose values, so she may not be able to feel when those levels drop when we look at her case. We also think about those very serious consequences of hypoglycemic unawareness for those patients that can't feel those lows coming on.

So, you would think about driving and whether or not the patient should be able to drive, or if they have work that includes operating heavy machinery. It can impact patients and their caregivers, as caregivers may be concerned about the patient living on their own. Or if you have a young patient who's going off to college, parents may be concerned about them being away from home and experiencing a severe hypoglycemic event. So, it can impact patients across all different types of diabetes and all different age levels.

Lawrence Herman: The other thing that patients don't always understand is that elevated glucose levels through some parts of the day do not protect you from hypoglycemia at other parts of the day, and people can have significant glycemic excursions in spite of the fact that they have hyperglycemia or a high finger stick at some point during their day.

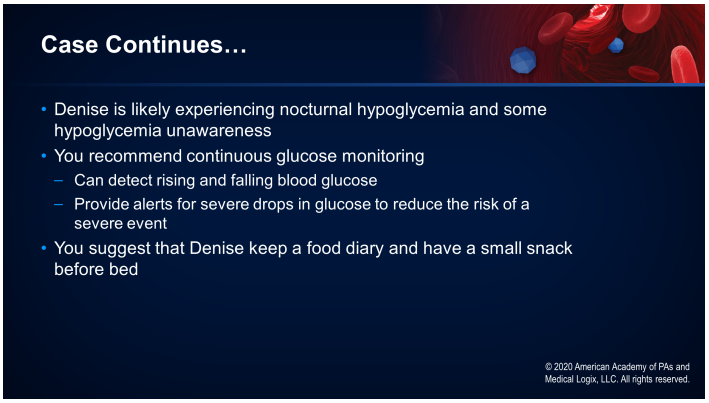


Let's review the last question, which asked, "What is the best approach with Denise to address her hypoglycemia?" The correct answer is (D), use continuous glucose monitoring to capture her blood glucose profile.

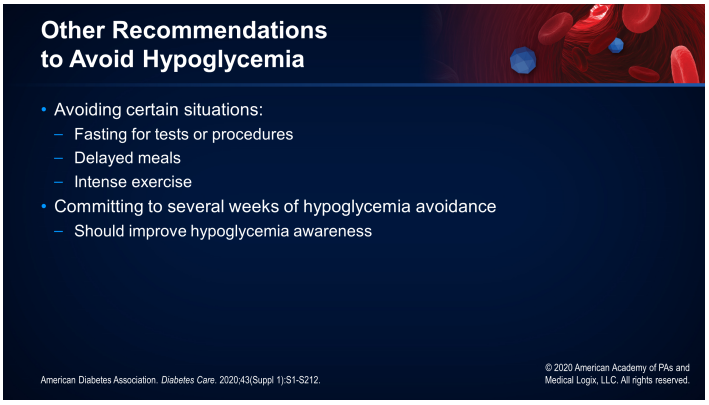
Based on Denise's symptoms, it's likely that she is experiencing nocturnal hypoglycemia with some degree of hypoglycemia

unawareness. She has mentioned that she is checking her blood glucose levels twice a day. You recommend that she begin continuous glucose monitoring, which should detect both rising and falling blood glucose values.

More frequent testing could detect any severe drops in glucose and provide an alert to Denise to reduce the risk of a severe hypoglycemic event, especially if she is experiencing hypoglycemia unawareness. She also agrees to keep a food diary and to have a small snack before bedtime to reduce her risk of nocturnal hypoglycemia.



You counsel Denise further on additional situations that could increase her risk of hypoglycemia, including fasting for other tests or procedures, delayed meals, and intense exercise. You remind her that several weeks of hypoglycemia avoidance should help to improve the hypoglycemia unawareness that she has experienced.



Now that we've addressed hypoglycemia, we need to think about an A1C goal for this patient. This brings us to our next clinical question.

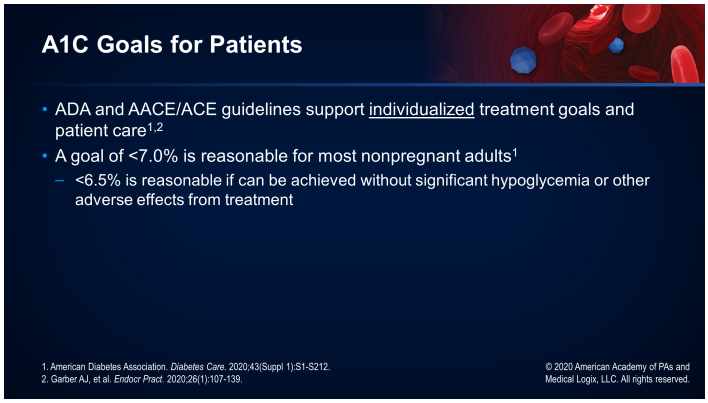
Question 3

Based on Denise's clinical presentation and history, what is an appropriate A1C goal?

A. Less than 6.5%
B. Less than 7%
C. Less than 7.5%
D. Less than 8%

When we look at guidelines, both in the United States and in Europe, one of the areas that they all agree on, the ADA as well as AACE guidelines, all support individualized treatment goals and patient care. The patient is the center of our focus, and goal decisions should be made with the patient reflecting their preferences, their needs, their values.

According to the ADA, a goal of less than 7% is reasonable for many nonpregnant adults, and a more stringent goal of less than 6.5% is reasonable if it can be achieved without significant hypoglycemia or other adverse effects of treatment.

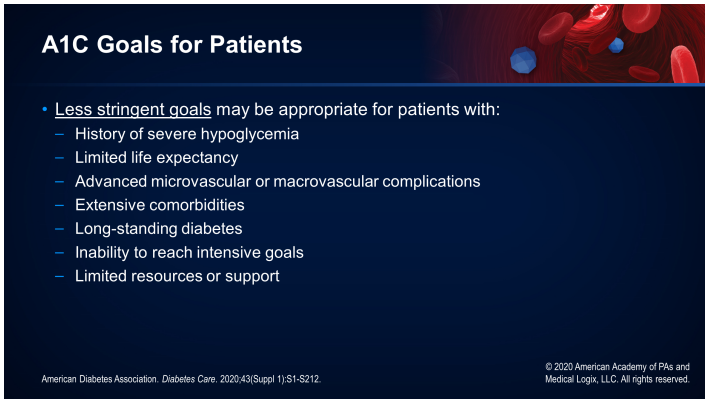


Melissa, can you walk us through your thought process as you determine how strict an A1C goal you want to see a particular patient achieve?

Melissa Murfin: Sure. It really depends on the patient and a lot of their individual characteristics. When you think about where to relax those goals and make them less stringent, several different types of patients may come to mind. So, for patients who have a history of severe hypoglycemia, a less stringent goal to make sure that they're not having those episodes may be quite appropriate for those patients. For folks who have a limited life expectancy, for some of our patients that already have some fairly advanced complications that are either microvasculature or macrovascular, so for any patient with extensive comorbidities.

Some of our patients with longstanding diabetes may not need the extensive or intensive goals, as well. And you also need to think about patients who may not have the capacity to reach those intensive goals.

And thinking also about our patients who have limited resources, limited support and access to potentially expensive products, like the glucose test strips when we're monitoring, or we just can't quite get them there without having several different expensive medications.

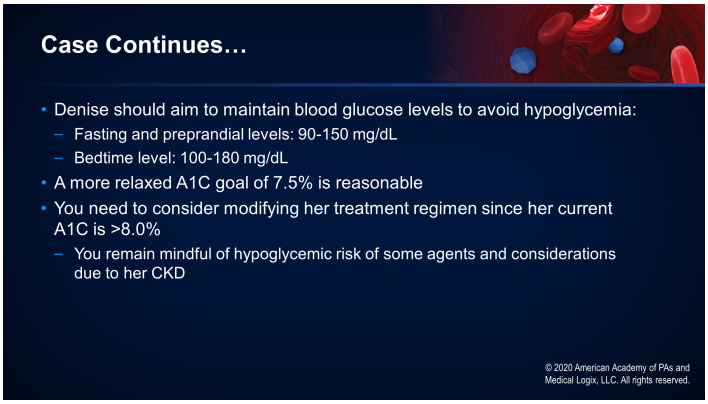


When we think about our patient Denise, she is a candidate for less stringent control based on her recent hypoglycemia and other comorbidities, as well.

Before we present more of Denise's case, let's quickly review the correct answer to this clinical question. An appropriate A1C goal for Denise based on her clinical history is less than 7.5%, indicating the correct answer is C. This would be appropriate based on her age, recent history of hypoglycemia, longstanding diabetes, and chronic kidney disease.

Maintaining a fasting and preprandial blood glucose level of 90 to 150 mg/dl and 100 to 180 mg/dl at bedtime is adequate in order to avoid additional hypoglycemic events.

Now let's continue the case. You both decide that a more relaxed goal of 7.5% is reasonable. Now that you've established a goal, you can begin to think about modifying her treatment regimen, since her A1C is currently above 8%. However, you also want to remain mindful of hypoglycemia risk with certain agents and the impact of chronic kidney disease on therapy selection.



This brings us to our next clinical question.

Question 4

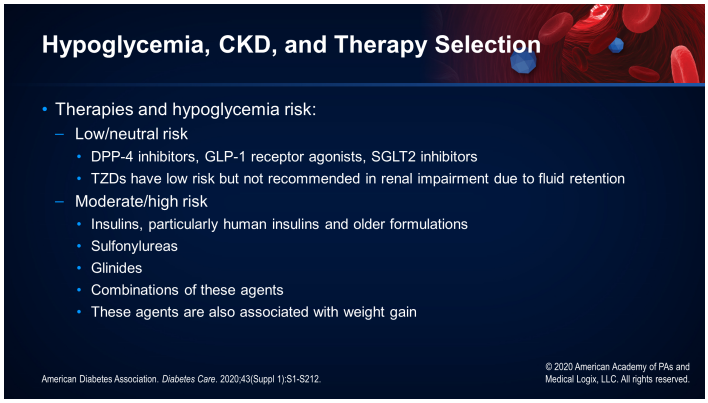
Which of the following therapies are associated with the highest risk of hypoglycemia?

A. Insulins and sulfonylureas
B. Dipeptidyl peptidase-4, or DPP-4 inhibitors, and glucagon-like peptide-1 receptor agonists, or GLP-1 RAs
C. Sodium glucose transporter-2 inhibitors, SGLT-2 inhibitors
D. Thiazolidinediones

Lawrence Herman: So let's take a moment and talk about the hypoglycemic risk as well as how that relates to CKD or renal function in general, remembering that, as renal function decreases and chronic kidney disease increases, hypoglycemia risk is based upon that level of kidney impairment or kidney function.

Now, the ADA and others have consensus statements regarding which drugs present the greatest or lower hypoglycemia risk, and the lowest or neutral risk are DPP-4 inhibitors, as well as GLP-1 RAs and SGLT-2 inhibitors.

TZDs tend to have a low risk, but they also are generally not recommended in renal impairment due to the potential for fluid retention, especially as the dose increases. Moderate to high risk would be insulins, particularly regular human insulins, the older insulins, less so with basal insulins and the newer insulins, and sulfonylureas, as well as glinides. And the worst combination would be insulins with a sulfonylurea, or SU.



The other issue is, these agents that I just mentioned are also associated with weight gain, something we try to avoid whenever we can. There are others that have restrictions specifically on renal function. Can you, with your pharmacology background, can you talk a little bit about that, especially, please?

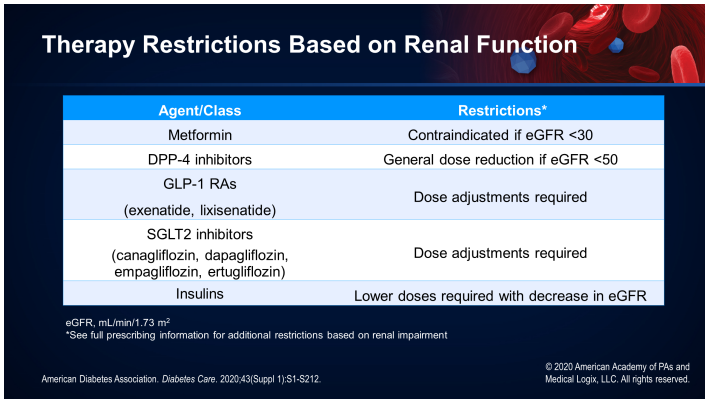
Melissa Murfin: Certainly. So, several of the agents actually have some restrictions based on renal function for patients. Metformin previously was restricted based on serum creatinine, but that has changed over the last few years, and now metformin is contraindicated based on EGFR below 30. So, we have a little bit more flexibility with metformin since that has changed.

The DPP-4 inhibitors generally recommend a dose reduction when EGFR drops below 50 mm/min/1.73 m^2. One of the DPP-4 inhibitors, linagliptin, has no dose restrictions based on renal function, but it's always a good idea to check when you're prescribing just to see if those doses need to be adjusted.

With the GLP-1 RAs, they do require dose adjustments for exenatide and lixisenatide, and just need to monitor with any increasing dose because of that acute kidney risk with the medications.

The SGLT-2 inhibitors do require dose adjustments for several of the different medications.

With insulins, you do have to keep in mind that doses may change as EGFR decreases for patients. So, you may need to adjust your insulin dose and actually lower it as the patient's renal function becomes more significantly impaired.

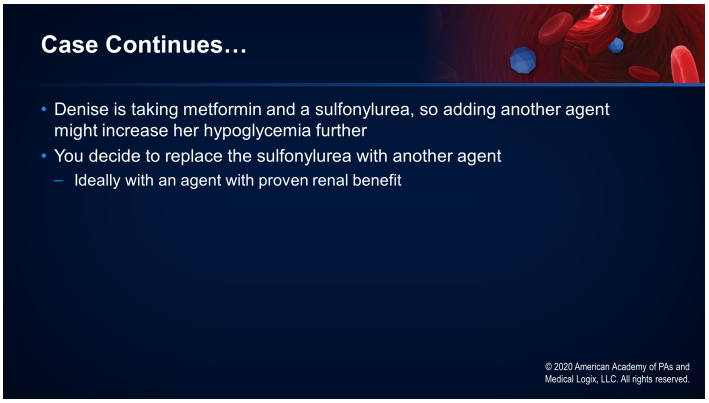


Lawrence Herman: Let's take a moment to review the correct answer to our clinical question. Which of the following therapies

is associated with the highest risk of hypoglycemia? The correct answer is (A), insulins and sulfonylureas. The other agents listed are all considered to have a low or neutral risk of hypoglycemia.

Because Denise is already taking metformin and a sulfonylurea, the addition of another agent might increase her hypoglycemia risk further. Additionally, you elect to replace the sulfonylurea with another agent, since Denise is experiencing hypoglycemic symptoms.

However, you also want to address her chronic kidney disease. You recall the specific agents within the GLP-1 RAs and SGLT-2 inhibitors have demonstrated cardiovascular and renal benefit in large clinical trials, and you initiate a discussion replacing the sulfonylurea with one of these agents.



This brings us to our last clinical question.

Question 5

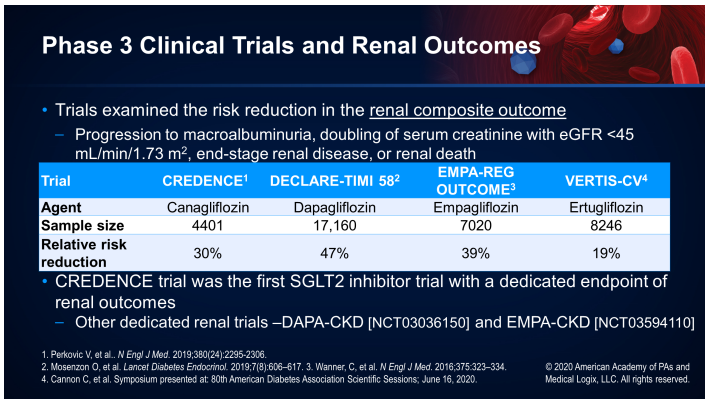
Which of the following agents has been studied in a dedicated renal outcomes trial, the CREDENCE trial, that showed a 30% risk reduction of the renal composite outcome?

A. Canagliflozin
B. Dapagliflozin
C. Empagliflozin
D. Ertugliflozin

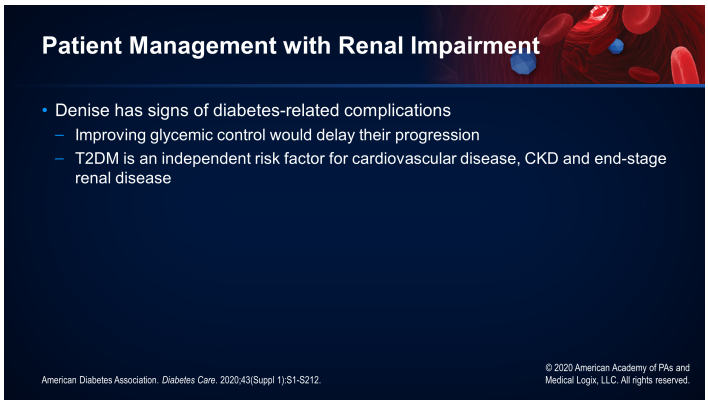
We've had several large, well-controlled phase 3 clinical trials that had examined the renal outcomes in both GLP-1 RAs and SGLT-2 inhibitors. And we can benefit by examining what those data say. Let's take a moment first to focus on the renal composite outcomes, which look at progression of renal disease, and we can measure that with macroalbuminuria or doubling of serum creatinine with an estimated GFR of less than 45, end-stage renal disease or renal death.

And basically, what we're looking at is to what extent the drug reduced the risk of these endpoints. And composite outcomes -- and these are large trials with between 4,400 and 17,000 patients -- but we have a relative risk reduction of between 19% all the way up to 47%, depending on the trial. Some are better than others, and you can see that from the slide that we are showing you now.

The CREDENCE trial of canagliflozin was the first dedicated endpoint of renal outcomes. There are, however, other dedicated renal outcomes trials that are ongoing, and that would include the DAPA-CKD trial and the EMPA-KIDNEY trial.

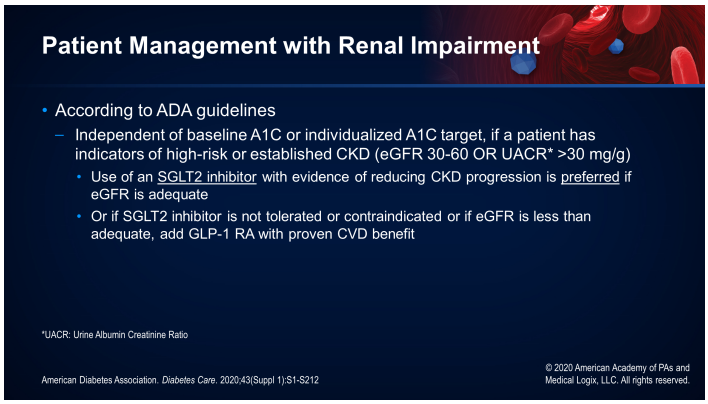


Melissa Murfin: So, coming back to our patient Denise, she has signs of diabetes-related complications, including nephropathy, and neuropathy. Improving glycemic control would delay progression of these complications, and type 2 in and of itself is an independent risk factor for cardiovascular disease and chronic kidney disease, as well as being a leading cause of end-stage renal disease. So, whatever we can do to help reduce those risks for her through her treatment plan would be very useful at this point.



The ADA guideline recommendations and the standards of care in 2020 suggest, independent of baseline A1C or the individualized A1C target, if a patient has indicators of high risk or has established chronic kidney disease with an EGFR of 30 to 60 or ACR of greater than 30 mg/g, the recommendation from the Diabetes Association is an SGLT-2 inhibitor that has evidence of reducing chronic kidney disease progression if the EGFR is adequate.

If the SGLT-2 inhibitor is not tolerated or is contraindicated for the specific patient, or if the EGFR is less than adequate, a GLP-1 receptor agonist with proven cardiovascular disease benefit can be added.



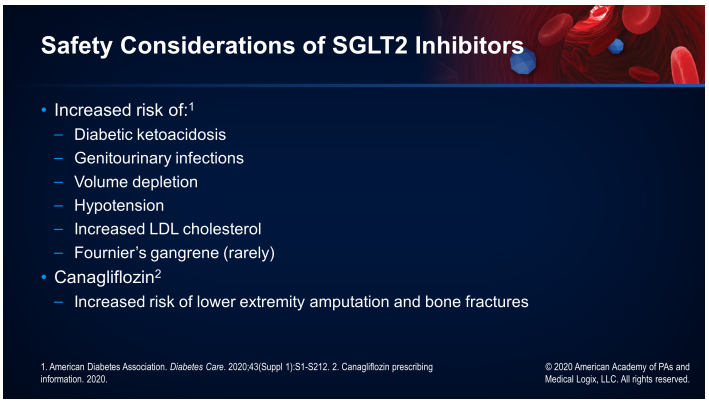
In this case, with Denise, SGLT-2 inhibitor would be preferred over the GLP-1 receptor agonist because of her chronic kidney disease.

Lawrence Herman: When you look at cardiovascular benefits, renal benefits - how do we make this decision? Is it based upon safety profiles? Is it based on weight? How do we ultimately come down on a particular drug?

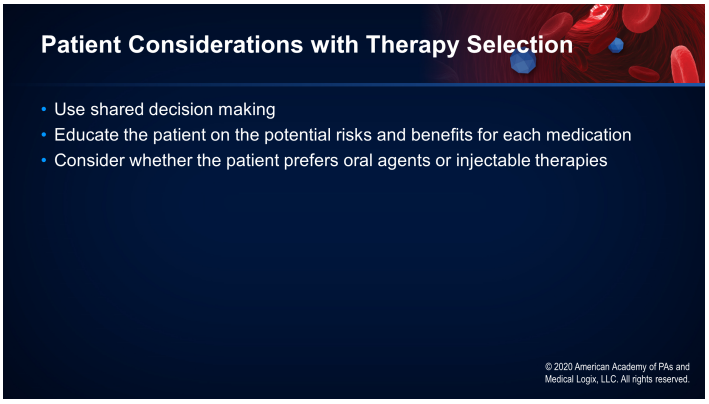
Melissa Murfin: So, you're correct. It is always a complicated decision and a process, and we do definitely look at those safety profiles. We need to look at the advantages and limitations of each individual therapy, and in particular, looking at all of these agents, they have, with the SGLT-2s, an increased risk of diabetic ketoacidosis. We're concerned about those genitourinary infections that have been associated with the class of medications.

We worry about volume depletion and dehydration with the medications, as well as hypotension. And there's that potential increase in LDL cholesterol with the SGLT-2 inhibitors. Much more rarely, they've been associated as a class with the Fournier's gangrene, which is a very unusual presentation of perineal gangrenous symptoms.

Canagliflozin, in particular, has also been associated with an increased risk of lower extremity amputation. Also, canagliflozin is specifically associated with the potential for bone fractures. We didn't see so much of that in the subsequent trials, like CREDENCE, but the warnings are still there and associated with the medication.



The other thing to think about is the patient, and what are the patient preferences? And always as PAs, we keep in mind that shared decision-making piece. So, making sure that a patient is aware of the potential risks and benefits for each medication is always important.

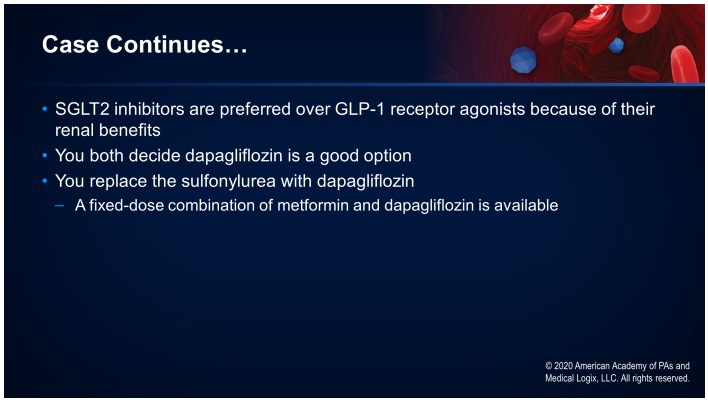


If the patient prefers to remain on oral agents, that would eliminate GLP-1 agonists, although the new oral semaglutide is available, so that may be an option if the patient does not want to use an injectable medication.

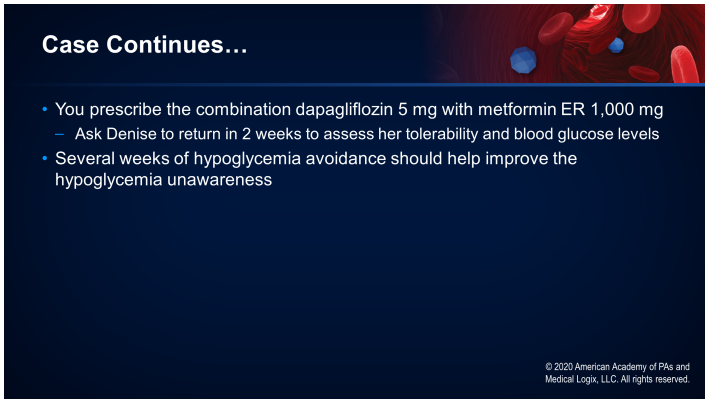
Returning to our question, canagliflozin was the agent evaluated in the CREDENCE clinical trial that showed a 30% risk reduction in the composite renal outcome, making the correct answer A.

You recognize that any of the SGLT-2 inhibitors would be suitable for Denise, and would be preferred over the GLP-1 receptor agonists because of their renal benefits. After discussing the potential advantages and limitations of therapies with Denise, you both decide that the SGLT-2 inhibitor dapagliflozin is a good option, because it has shown the greatest reduction in CKD progression in clinical trials and is not associated with some of the more serious adverse effects.

Our case continues with a discussion with Denise regarding the replacement of the sulfonylurea with dapagliflozin. You mentioned that a fixed-dose combination of metformin and dapagliflozin is available, and Denise is receptive to reduce her overall medication burden.

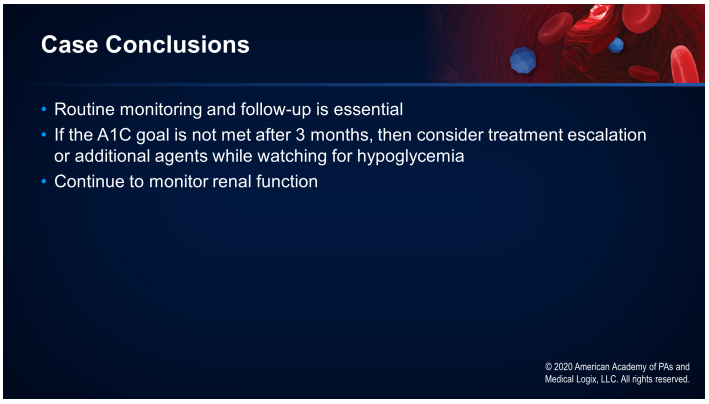


You prescribe the once-daily combination of dapagliflozin 5 mg with metformin ER 1,000 mg, the recommended starting dose, and ask Denise to return in 2 weeks to assess her tolerability and blood glucose levels. You remind her that several weeks of hypoglycemia avoidance should help to improve the hypoglycemia unawareness that she has experienced.



Lawrence Herman: As we bring our case to a close, we should remember that routine monitoring and follow-up is essential. If Denise does not reach her A1C goal after 3 months with the new therapeutic regimen, then treatment can be escalated further to increase the dosage of dapagliflozin combination, or additional

agents can eventually be added with a constant watch for hypoglycemia symptoms.



In the long term, you plan to monitor her renal function, because this combination is not recommended for patients with an estimated GFR below 45.

I would like to thank our expert, PA Dr. Melissa Murfin, for your great insights and discussion. And I would like to thank you, our audience, for participating in this *eCase Challenge* on hypoglycemia in special populations.

CLINICAL PEARL

We hope you have enjoyed this *eCase Challenge* and that you have increased your knowledge and confidence in the diagnosis and management of type 2 diabetes in special patient populations.

PAs should remember that hypoglycemia is a common event in patients with type 2 diabetes and remains the major limiting factor in optimal glycemic management. Importantly, PAs should ask patients at risk about any symptomatic and asymptomatic hypoglycemia at every visit.

Patients diagnosed with type 2 diabetes often have multiple and significant comorbidities, including cardiovascular disease. PAs should review the patient history and remain cognizant of comorbidities when deciding on a therapeutic regimen and A1C goals.

Recent clinical trials of agents within the GLP-1 RA and SGLT-2 inhibitor classes have demonstrated cardiovascular benefit for multiple agents, and agents with proven benefit are recommended for patients at high risk or with established atherosclerotic cardiovascular disease.

Given the cardiovascular benefit of some agents, PAs should include these agents when appropriate to improve cardiovascular outcomes and reduce major cardiovascular events that contribute to mortality and morbidity in this patient population. Thank you again for your participation in this *eCase Challenge*.

References:

Alsahi M and Gerich J. Hypoglycemia, Chronic Kidney Disease, and Diabetes Mellitus. *Mayo Clin Proc.* 2014;89(11):1564-1571.

American Diabetes Association. Standards of Medical Care in Diabetes – 2020. *Diabetes Care.* 2020;43(Suppl 1):S1-S212.

Canagliflozin prescribing information. 2020. Janssen Pharmaceuticals; Titusville, NJ.

Cannon C, McGuire D, Cherney D, et al. Results of the eValuation of ERTugliflozin Efficacy and Safety CardioVascular Outcomes Trial (VERTIS CV). Symposium presented at: 80th American Diabetes Association Scientific Sessions; June 16, 2020.

Garber AJ, Handelsman Y, Grunberger G, et al. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2020 EXECUTIVE SUMMARY. *Endocr Pract.* 2020;26(1):107-139.

KDIGO. Summary of recommendation statements. *Kidney Int.* 2013;3(1):1-150.

Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol.* 2019;7(8):606–617.

Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med.* 2019;380(24):2295-2306.

Suh S and Kim J. Glycemic Variability: How Do We Measure It and Why Is It Important? *Diabetes Metab J.* 2015;39:273-282.

Unger J. Uncovering undetected hypoglycemic events. *Diabetes Metab Syndr Obes Targets Ther.* 2012;5:57-74.

Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med.* 2016;375:323–334.

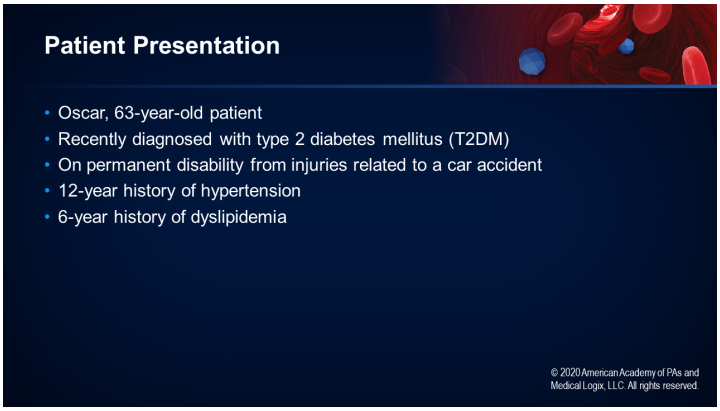
Yun J-S and Ko S-H. Risk Factors and Adverse Outcomes of Severe Hypoglycemia in Type 2 Diabetes Mellitus. *Diabetes Metab J.* 2016;40:423-432.

eCASE CHALLENGE #2

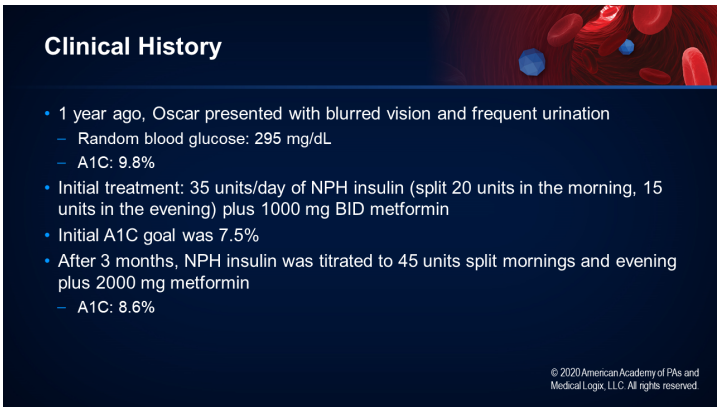
Lawrence Herman, DMSC(c), MPA, PA-C, DFAAPA: Hello, and welcome to this video *eCase Challenge*, "Individualized Management of Patients with Type 2 Diabetes and Comorbidities: Reducing Hypoglycemia Risk." I'm Lawrence Herman, a PA, President of Palantir Healthcare LLC in Boiling Springs, South Carolina, and a Past President of the American Academy of PAs in Alexandria, Virginia.

Joining me today is Dr. Melissa Murfin, a PA and Associate Professor, Research Coordinator in the Department of Physician Assistant Studies at Elon University in North Carolina. This CME activity consists of two *eCase Challenges*. This is our second *eCase Challenge*, and our patient is Oscar. So, let's get started with our second case.

Oscar is a 63-year-old patient who was recently diagnosed with type 2 diabetes mellitus and is on permanent disability from injuries sustained in an automobile accident 3 years ago. He comes to you today because he recently moved to a new location and needed to switch providers. He has a documented 12-year history of hypertension and a 6-year history of dyslipidemia.



About a year ago, Oscar presented to his provider with blurred vision and frequent urination. A random blood glucose at the time was 295 mg/dl, and his A1C level was 9.8%. Because of his severe hyperglycemia and Medicare coverage, his initial treatment was 35 units/day of NPH insulin split 20 units in the morning and 15 units in the evening, and 1,000 mg BID of metformin.

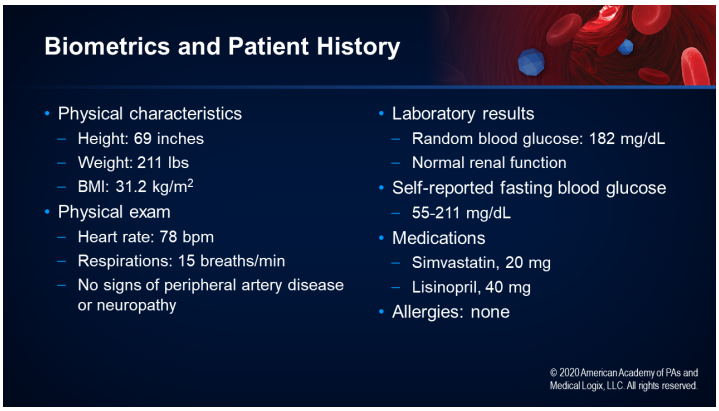


An initial A1C goal of 7.5% was decided to balance his age and risk factors with the severe hyperglycemia, hypertension, and dyslipidemia. After 3 months of titrating his insulin to 45 units of NPH insulin split mornings and evenings, and 200 mg of metformin, Oscar's A1C was 8.6%. He is in the office today for a checkup.

Oscar's medical chart reveals that he is considered obese based on his BMI.

On physical exam, his heart rate is slightly elevated, and his respirations are normal. He does not have any evidence of peripheral artery disease or peripheral neuropathy. A random blood glucose test shows a level of 182 mg/dl.

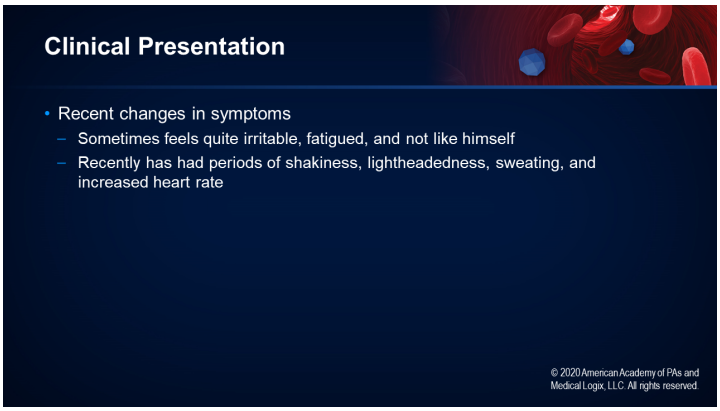
He self-reports fasting blood glucose levels that range from 55 to 211 mg/dl. Previous lab results show his renal function is normal. In addition to his current insulin and metformin regimen, Oscar also takes a statin to manage his hypercholesterolemia and an ACE inhibitor to manage his hypertension. He has no known allergies.



Oscar's family history shows that his mother has a history of cardiovascular disease and suffered a fatal myocardial infarction at the age of 76 years. His sister also shares a history of hypertension and dyslipidemia. He lives with his wife, is a former smoker and does not consume any alcohol.

Overall, his physical activity is limited because of his prior injuries and limited mobility. While he has tried to maintain a healthier diet since his diabetes diagnosis, he finds it challenging to prepare healthy meals and comments that he often skips breakfast.

During the visit, you ask Oscar if he has any questions about his current therapy or if he has experienced any changes in his symptoms. He indicates that he sometimes feels quite irritable and fatigued and not like himself. He also reports that he has recently had periods of shakiness, with lightheadedness, sweating and an increased heart rate.



This brings us to our first clinical question.

Question 1

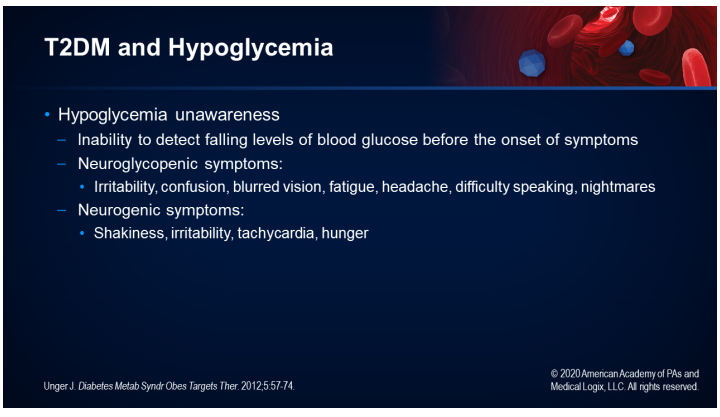
Based on Oscar's clinical presentation and history, which of the following conditions is a likely cause of his recent symptoms?

A. Arrhythmia
B. Hypoglycemia unawareness
C. Hypotension
D. Vertigo

Oscar's symptoms likely indicate that he is experiencing hypoglycemia and, to some degree, hypoglycemia unawareness. And that's the inability to detect his falling levels of blood glucose before he actually has symptoms occur.

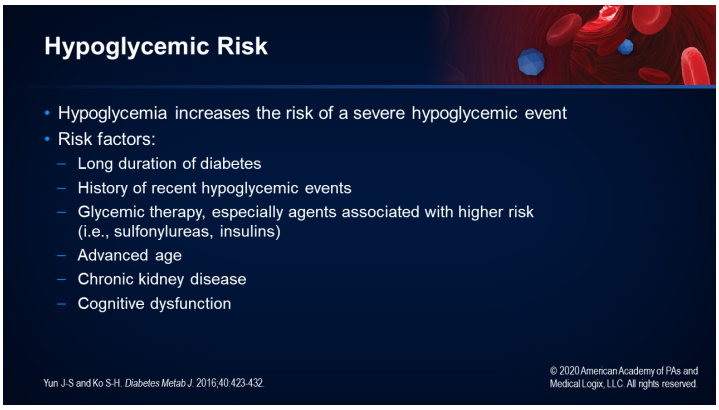
And the neuroglycopenic symptoms are things like irritability, confusion, blurred vision. He may be fatigued, or headache. He may have difficulty speaking. He may wake up saying that he's had nightmares. And that can all occur prior to autonomic symptoms.

The neurogenic symptoms are things like shakiness and irritability, rapid heartbeat. He may experience some hunger.



Hypoglycemia puts patients at a greater risk for having a severe hypoglycemic event, and those risk factors are things like a long duration of diabetes; recent history of prior hypoglycemic events; depending upon what agents the patient may be on for glycemic therapy, especially insulins and sulfonylureas; advancing age -- and that depends upon the patient's general health, but certainly anyone over the age of 50 and older, depending on their health, could be at risk; the incidence of kidney disease that they have; as well as a baseline level of cognitive dysfunction.

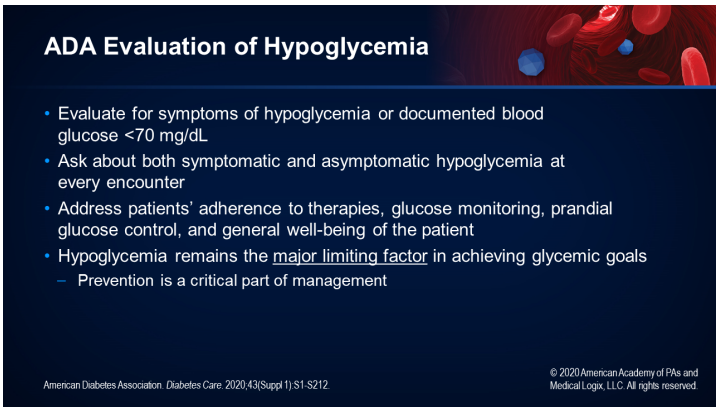
Now, the ADA has some standard to evaluate this. Melissa, can you review those for a second?



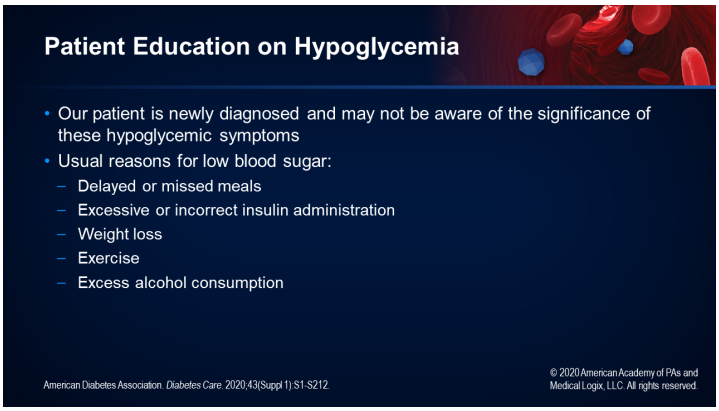
Melissa Murfin, PA-C, PharmD, BCACP: Sure thing. I'd be happy to. So, the recommendation from the American Diabetes Association is to evaluate patients for symptoms of hypoglycemia or documented blood glucose drops below 70 mg/dl. The Diabetes Association recommends that clinicians ask about both symptomatic and asymptomatic hypoglycemia at every encounter, so it's important for us to remember to ask those questions for each patient.

We also need to look at adherence to their medications or their other therapies, look at their glucose monitoring, their prandial glucose control, and the overall well-being of the patient.

We want to keep all these things in mind, because hypoglycemia is the major limiting factor in achieving glycemic goals in patients with type 2 diabetes, and prevention is a critical part of managing that hypoglycemia.



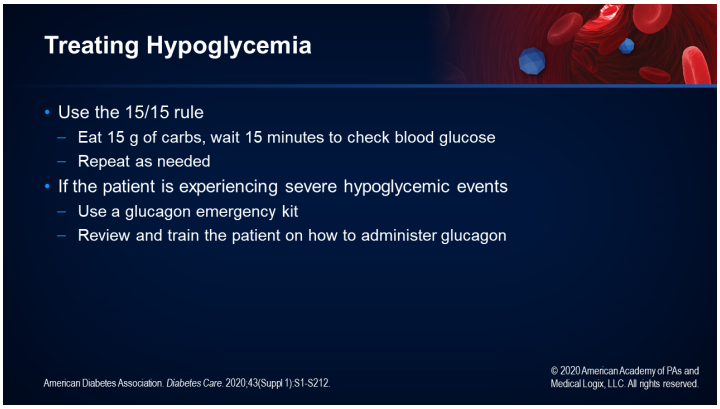
For our patient Oscar, we have to remember, he is newly diagnosed with type 2 diabetes, so may not even be aware of the significance of these hypoglycemic symptoms. That's a good place to start, with patient education on hypoglycemia, and to help explain those reasons for low blood sugar so the patient is aware.



Some of those may happen as a result of delaying or missing meals, excess or incorrect insulin administration. A weight loss actually can bring on hypoglycemias. It may change the patient's required doses of their medications. Exercise can also precipitate hypoglycemia, as well as excess alcohol consumption.

Lawrence Herman: Would you remind our audience, with a patient like Oscar, how to treat hypoglycemia?

Melissa Murfin: Absolutely. You use the 15/15 rule -- eat 15 g of carbohydrates and then wait 15 minutes to check blood glucose. And then you can repeat that as needed. If the patient is experiencing severe hypoglycemic events, they'll need a glucagon emergency kit to have on hand for those severe episodes.

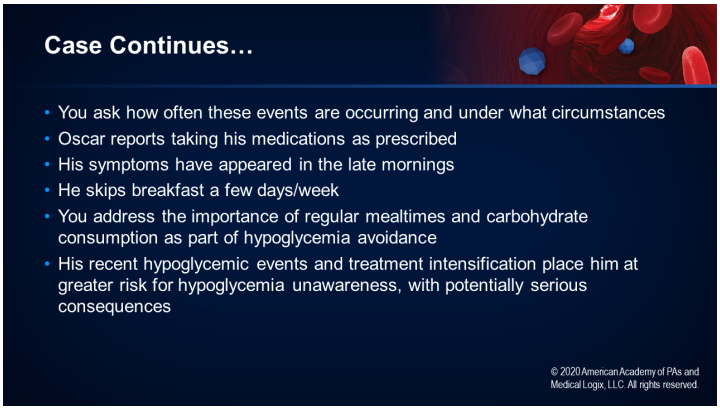


Let's review the question posed, which asked, which of the following conditions is a likely cause of Oscar's recent symptoms? The correct answer is (B), hypoglycemia unawareness. Oscar's symptoms are consistent with hypoglycemia with some degree of hypoglycemia unawareness.

You ask him how often these events are occurring and under what circumstances.

Oscar reports that he is taking his insulin and metformin as prescribed and that his symptoms have appeared in the late mornings. When you ask how frequently he skips breakfast, he states at least a few days per week. Because you've learned that he is skipping meals, you address the importance of regular mealtimes and carbohydrate consumption as part of hypoglycemia avoidance.

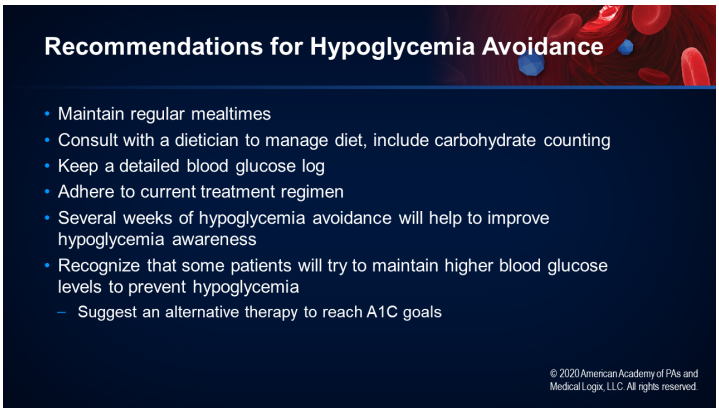
You explain to Oscar that his recent hypoglycemic events and treatment intensification put him at greater risk for hypoglycemia unawareness, which can result in a severe hypoglycemic event with potentially fatal consequences.



You instruct Oscar that over the next few weeks, it will be really important to maintain regular mealtimes and consult with a dietitian to better manage his dietary patterns, including how to count carbohydrates.

You also suggest that he keep a detailed blood glucose log and adhere to his current treatment regimen to avoid additional hypoglycemic events. You explain that several weeks of hypoglycemia avoidance will help to improve the hypoglycemia unawareness that he has experienced. Oscar expresses that he is fearful of having any more hypoglycemic events, and he agrees to be more consistent with meals.

As his provider, you recognize that some patients will begin to maintain higher blood glucose levels than what is recommended to prevent the unpleasant effects of hypoglycemia. You suggest that an alternative pharmacologic therapy be used to reach his A1C goals and avoid additional hypoglycemic events.



This brings us to our next clinical question.

Question 2

Which of the following changes to Oscar's current treatment regimen would help him avoid future hypoglycemia and maintain a high level of efficacy in reducing A1C?

A. Decrease the NPH insulin by 5 units and add 5 units of a rapid-acting insulin.
B. Replace the NPH insulin with a GLP-1 receptor agonist.
C. Replace the NPH insulin with a basal insulin analog.
D. Replace the NPH insulin with a DPP-4 inhibitor.

Lawrence Herman: We have a whole host of treatment options that are available to us, and we want to balance the risk of hypoglycemia, minimizing that, with maintaining the highest level of efficacy in terms of A1C lowering that we can achieve.

Agents that are associated with a higher risk of hypoglycemia are glinides, sulfonylureas and the older insulins. Basal insulins still have some degree of hyperglycemic risk, but less so than regular and NPH insulins. Agents that have a lower risk of hypoglycemia are the DPP-4 inhibitors, the SGLT-2 inhibitors, the GLP-1 RAs as well as TZDs.

Consider those drugs or classes when there's a compelling need to minimize hypoglycemia.

In many patients, GLP-1 RAs can be considered prior to initiating insulins, and we have a need to evaluate both the advantages and limitations of each of these therapies. As we know, every drug has a risk, a benefit, and an alternative associated with it.

Hypoglycemia Risk and Therapies

- Want to minimize hypoglycemia risk but maintain the highest level of efficacy (A1C lowering) possible
- Moderate/high risk:
  - Glinides
  - Sulfonylureas
  - Insulins, particularly older formulations, regular human insulin and NPH insulin
- Low/neutral risk:
  - DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists (GLP-1 RAs)
  - Thiazolidinediones (TZDs)
- GLP-1 RAs can be considered prior to initiating insulins

American Diabetes Association. *Diabetes Care*. 2020;43(Suppl 1):S1-S212.

Now, there are specific clinical characteristics of these agents. Melissa, would you take a moment to remind us of those, please?

Melissa Murfin: Certainly. So, looking at the drugs by class, the SGLT-2 inhibitors are associated with a lower hypoglycemic risk as well as weight loss, and are intermediate in efficacy in terms of A1C lowering. As a class, the drugs are also associated with some risks, such as bone fractures, diabetic ketoacidosis, genitourinary infections, hypotension, and increased LDL. Canagliflozin has a warning for amputation risk.

The GLP-1s are associated also with low hypoglycemia and with weight loss and are fairly effective in terms of A1C lowering. They do carry a boxed warning for thyroid C-cell tumors, which were evidenced primarily in studies in rats and haven't been really associated in human trials. These drugs, the GLP-1s, do have a risk of GI side effects and injection site reactions, as these are injectable medications.

The DPP-4s have an intermediate ability to lower blood glucose, low hypoglycemic risk and are relatively weight neutral. So, they're not going to cause weight gain in patients. They are associated with the risk of acute pancreatitis and joint pain.

The TZDs are pretty effective in lowering A1C and have a low hypoglycemic risk, but are associated with weight gain, and that can be problematic for patients. They do carry a boxed warning for heart failure concerns with the medications, as well as fluid retention, bone fractures and increased LDL.

Key Characteristics of Agents

Agent	Efficacy	Hypo. risk	Weight change	Other considerations
SGLT2 inhibitors	Intermediate	Low	Loss	Risk of amputation, bone fractures, DKA, GU infection, hypotension, increased LDL cholesterol
GLP-1 RAs	High	Low	Loss	Boxed warning: thyroid C-cell tumors; GI side effects, injection site reactions
DPP-4 inhibitors	Intermediate	Low	Neutral	Risk of acute pancreatitis, joint pain
TZDs	High	Low	Gain	Boxed warning: HF with certain agents Fluid retention, bone fractures, increased LDL cholesterol

American Diabetes Association. *Diabetes Care*. 2020;43(Suppl 1):S1-S212.

In this case, with our patient Oscar, a GLP-1 would be preferred because of its high efficacy, low hypoglycemia risk, and associated weight loss. A DPP-4 inhibitor is not quite as efficacious as we need in lowering the A1C, and decreasing dosage of the NPH insulin or adding a rapid-acting insulin is likely not going to change the hypoglycemia risk. Generally, those non-insulin drugs are going to lower the A1C by about 0.7 to 1%.

Case Continues…

- In our patient, a GLP-1 RA would be preferred because of its:
  - High efficacy
  - Low hypoglycemia risk
  - Associated weight loss
- DPP-4 inhibitor is not as efficacious
- Decreasing NPH dosage or adding rapid-acting insulin is not sufficient to change hypoglycemia risk

Lawrence Herman: Let's go back and review the question which asked which of the following changes to Oscar's current treatment regimen would help him avoid future hypoglycemia and maintain a high level of efficacy in reducing A1C? The correct answer is (B), replace the NPH insulin with a GLP-1 RA.

Case Continues…

- You initiate a conversation about advantage and limitations of therapies
- You recall that certain agents provide cardiovascular benefits

You initiate a conversation with Oscar about the potential advantages and limitations of therapies with a lower hypoglycemic risk. In addition, you recall that certain agents can also provide cardiovascular benefit to patients.

This brings us to our next clinical question.

Question 3

Which of the following treatment approaches accurately reflect the current 2020 recommendations by the ADA for the use of agents in patients at risk or with established atherosclerotic cardiovascular disease?

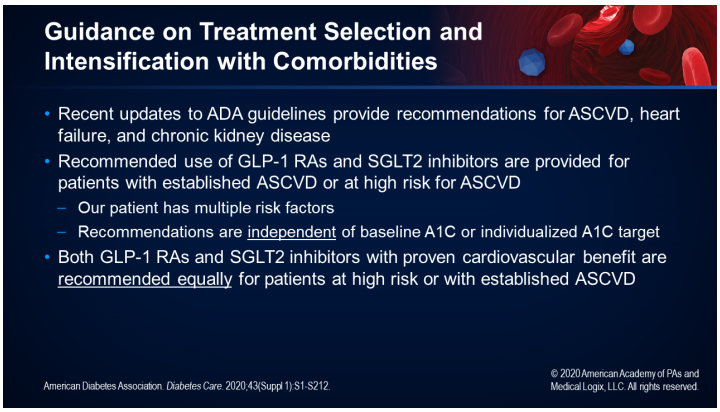
A. DPP-4 inhibitors are preferred over other classes of agents for ASCVD.
B. GLP-1 RAs and DPP-4 inhibitors are recommended in patients at high risk or with established ASCVD.
C. GLP-1 RAs and SGLT-2 inhibitors are only recommended if baseline A1C is greater than 9.0%.
D. GLP-1 RAs and SGLT-2 inhibitors with proven CVD benefit are recommended equally.

Now, there have been recent updates to ADA guidelines which provide specific guidance on treatment selection and intensification based on comorbidities. And I think that is a very good thing in a very confusing landscape here.

Most notably, ASCVD, heart failure and chronic kidney disease come into play in terms of treatment selection. The use of GLP-1 RAs or SGLT-2 inhibitors are provided for patients who have established ASCVD or indications of high-risk ASCVD.

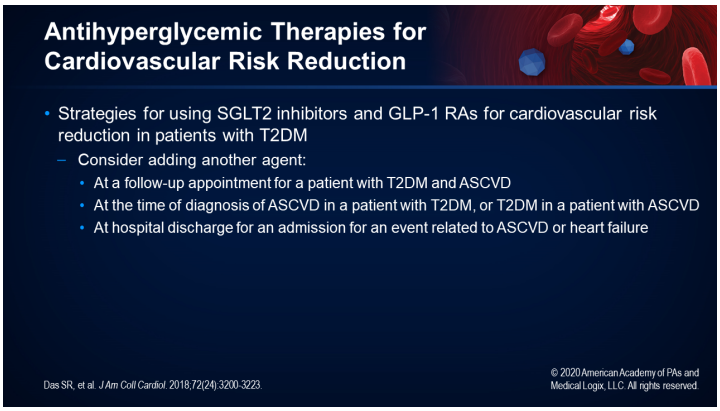
And Oscar has multiple important risk factors, including his family history, his older age, the fact that he's hypertensive, he has dyslipidemia, he's obese. The recommendation for the use of these agents is independent of baseline A1C or what his individualized A1C target may be.

Currently, both GLP-1 RAs and SGLT-2 inhibitors with proven cardiovascular disease benefit are recommended equally for patients at high risk or with established ASCVD.



Now, the American College of Cardiology Expert Consensus Discussion Pathway also focuses on broad strategies for using SGLT-2 inhibitors and GLP-1 RAs for CV risk reduction in type 2 diabetes. And the scenarios in which the clinician may consider starting another agent include the following.

You can do this at a follow-up appointment for a patient with type 2 diabetes and ASCVD. We do this at the time of diagnosis of ASCVD in a patient with type 2 diabetes or type 2 diabetes in a patient with ASCVD, or at hospital discharge for an admission for an event related to ASCVD, or -- and this is important -- heart failure.

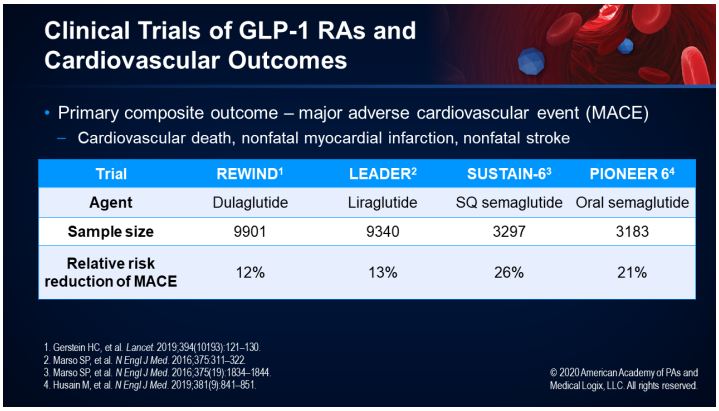


Several large-scale clinical trials have demonstrated CV benefit in these agents, and the primary outcomes here are MACE, cardiovascular death, nonfatal MI and nonfatal stroke. So MACE is the important one, but we also need to include heart failure, which is becoming increasingly frequent in this country.

Melissa, would you take a moment and give us a brief review, not a deep dive, but a brief review of the randomized trials associated with GLP-1 RAs and the reduction of MACE?

Melissa Murfin: Sure, I'd be happy to. So there were several trials that looked at GLP-1s in terms of their ability to reduce MACE, the REWIND trial, the LEADER trial, the SUSTAIN-6 trial and the PIONEER 6 trial. So these covered a number of different patient groups, all the way from close to 3,200 patients up to about 9,900 patients. So fairly good sample sizes.

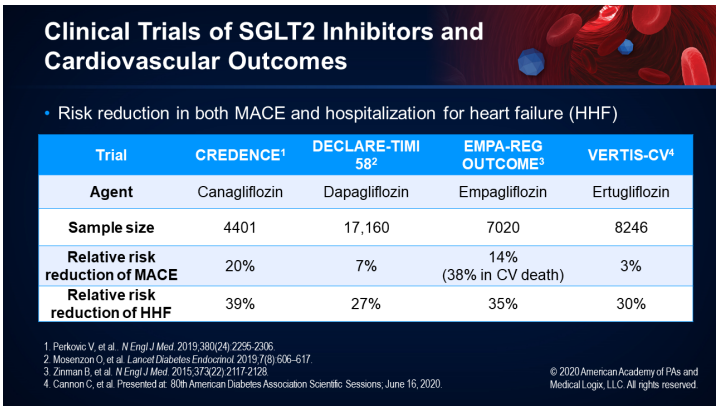
And what they showed for the GLP-1s was a reduction in the risk of MACE of anywhere from 12 to 26%. So pretty significant numbers there based on these trials.



We can also look at the SGLT-2 inhibitors and look at how they reduce MACE in terms of particular trials that study those drugs, as well. So those are trials like CREDENCE, DECLARE, EMPA-REG and the VERTIS-CV trials. And those trials were much larger, with larger patient populations, so anywhere from about 4,400 patients to about 17,000 patients. So, very significant patient numbers there.

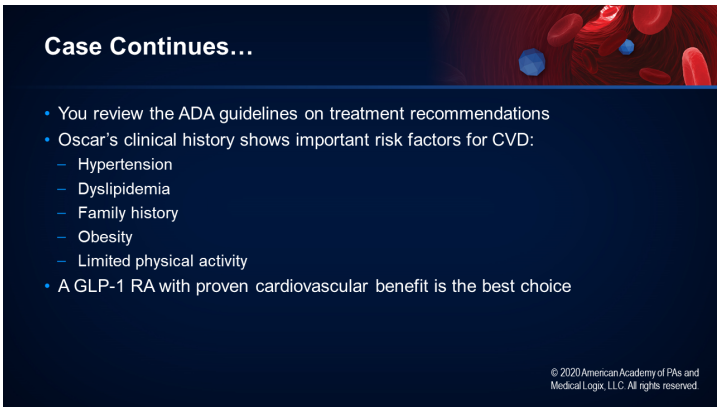
And across the board with these four different trials, the relative risk reduction of MACE in these patient populations was anywhere from 3% to 20%. One trial in particular showed a 38% reduction in cardiovascular death. So very significant numbers there for both the GLP-1 agonists and the SGLT-2 inhibitors.

We also can look at heart failure in terms of the SGLT-2s, as these studies included that as an outcome. And the relative risk reduction for heart failure was anywhere from 27% to 39%. So the heart failure risk is significantly improved, as well, and -- in the SGLT-2 inhibitors.



Lawrence Herman: Let's return to the clinical question, which asked, which of the following treatment approaches accurately reflects the current 2020 recommendations by the ADA for the use of agents in patients at risk or with established atherosclerotic cardiovascular disease? The correct answer is (D), GLP-1 RAs and SGLT-2 inhibitors with proven CVD benefit are recommended equally.

You review the ADA guidelines on treatment recommendations. You note from Oscar's clinical history that he does have some important risk factors for cardiovascular disease, including hypertension, dyslipidemia, family history, obesity, and limited physical activity, confirming that a GLP-1 RA is likely the best choice for this patient, given the other advantages discussed previously and the potential cardiovascular risk benefit.



You know that based on clinical trial data, a number of therapies have expanded their FDA indications. This brings us to our next clinical question.

Question 4

Which of the following GLP-1 RAs is the only agent in its class to have an approved indication for both primary and secondary prevention of atherosclerotic cardiovascular disease?

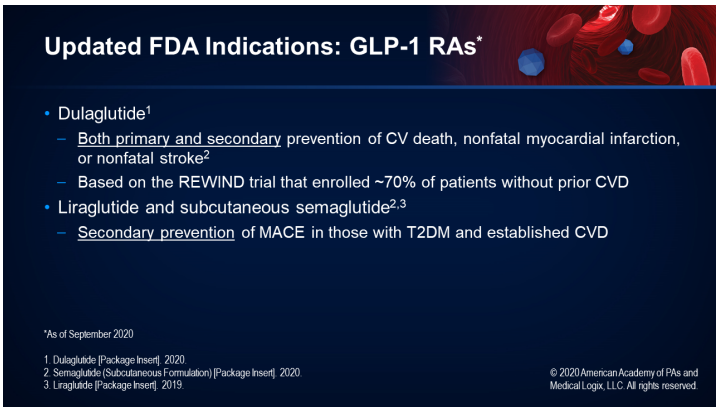
A. Dulaglutide
B. Liraglutide
C. Oral semaglutide
D. Subcutaneous semaglutide

We know cardiovascular disease is the leading cause of death and disability in patients with diabetes, and that diabetes-associated cardiovascular disease accounts for $37.3 billion in healthcare spending annually.

In the last 20 years, the risk for adverse CV events has remained largely unchanged, while the prevalence of type 2 diabetes has dramatically increased.

Only dulaglutide is indicated to reduce the risk of CV death, nonfatal MI or nonfatal stroke in both primary and secondary prevention patients. Based on the REWIND trial, the largest primary prevention cohort of any cardiovascular outcomes trial in any antihyperglycemic agent, nearly 70% of the patients in REWIND did not have a prior CV event or disease that was identified.

GLP-1 RAs, which at this time include liraglutide and subcutaneous semaglutide, and are approved for an additional indication of reducing the risk of MACE in patients with type 2 diabetes and established cardiovascular disease -- in other words, secondary prevention.



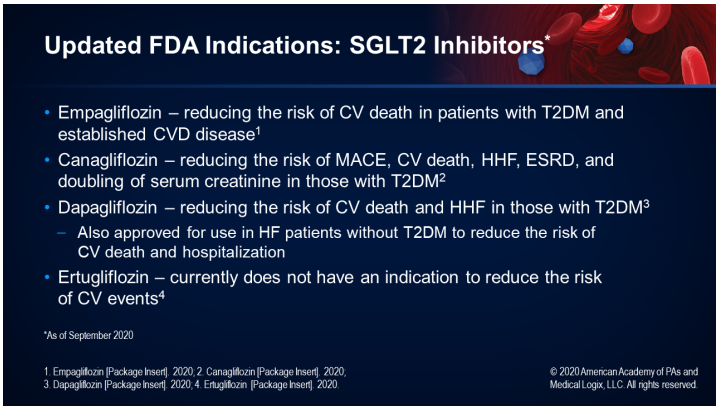
Melissa, can you talk to us a little bit about SGLT-2 inhibitors, because they have a different indication?

Melissa Murfin: Sure. The SGLT-2 inhibitors have different cardiovascular indications for patients with type 2 diabetes and comorbid cardiovascular disease. Empagliflozin has the indication for reducing the risk of cardiovascular death in patients with type 2 diabetes and established cardiovascular disease.

Canagliflozin has an indication for reducing the risk of MACE, and later for reducing the risk of cardiovascular death, heart failure, end-stage renal disease and doubling of serum creatinine.

Dapagliflozin has an indication for reducing the risk of cardiovascular death and heart failure. This also carried an approval for patients with heart failure without type 2 diabetes to help reduce the risk of cardiovascular death and hospitalization.

Ertugliflozin has a relative risk reduction for MACE in clinical trials, but has not currently been associated with an indication on the FDA labeling to reduce the risk of cardiovascular events. There are multiple ongoing trials to evaluate the GLP-1 RAs and SGLT-2 inhibitors in both primary and secondary prevention.



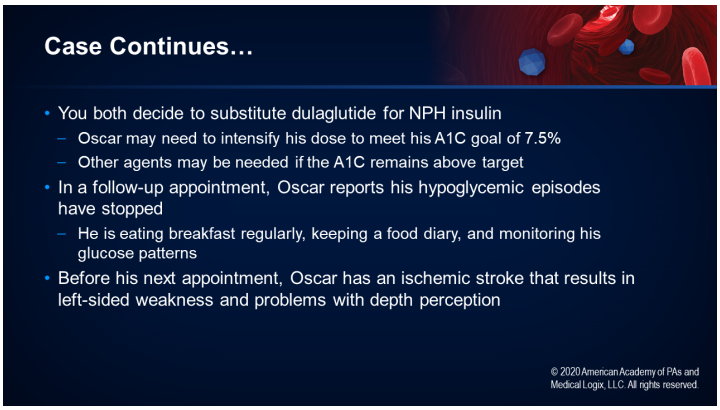
So, let's review the answer to our clinical question. Which of the following GLP-1 RAs is the only agent in its class to have an approved indication for both primary and secondary prevention of ASCVD? The correct answer is (A), dulaglutide.

After discussing treatment options with Oscar, you both decide that substituting the dulaglutide for the NPH insulin is an appropriate choice. The recommended starting dose is 0.75 mg once weekly. However, you recognize that he may need to intensify this dose to 1.5 mg once weekly and/or add other agents to lower his A1C to the goal of 7.5%.

Current ADA guidelines indicate that other agents -- mainly the SGLT-2 inhibitors with proven cardiovascular disease benefit or

other agents demonstrating cardiovascular safety -- should be added if the A1C remains above target.

You schedule a follow-up appointment for 2 weeks later. Oscar returns to the office after that time and reports that he has not had any additional hypoglycemic episodes. He's been eating breakfast regularly in the mornings and keeping a food diary. He's been more carefully monitoring his blood glucose patterns, which now range from 82 to 179 mg/dl. You ask Oscar to return to the office in 3 months to check his A1C.



Before his next appointment, Oscar has an ischemic stroke that results in left-sided weakness and problems with depth perception. He returns to the office for a well visit checkup and to determine if any changes to his therapeutic regimen are warranted.

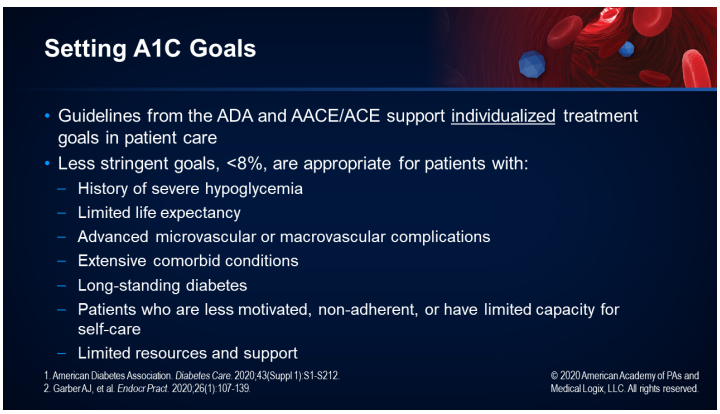
This brings us to our final clinical question.

Question 5

Based on Oscar's recent cardiovascular event, what is an appropriate A1C goal now?

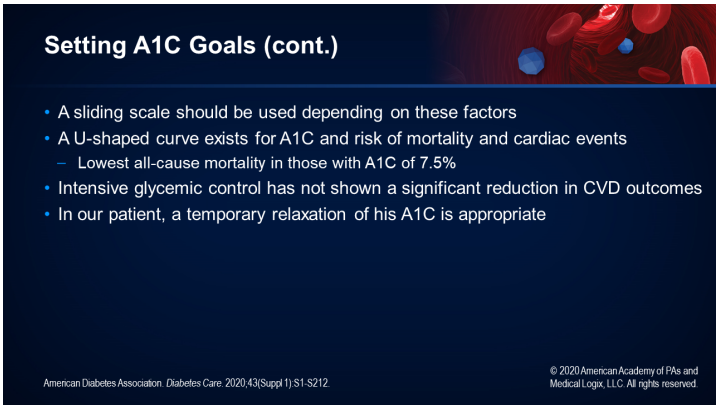
A. Less than 6.5%
B. Less than 7%
C. Less than 7.5%
D. Less than 8%

Lawrence Herman: Current guidelines from the ADA as well as AACE support individualized treatment goals in patient care. And less stringent A1C goals -- and what I mean by that is an A1C of less than 8% -- would be appropriate for patients with things such as a history of severe hypoglycemia; someone with a limited life expectancy; someone who has advanced micro- or macrovascular complications; someone who has extensive comorbid conditions; individuals with long-standing diabetes; patients who are either less motivated, nonadherent, have limited capacity for self-care; or they have limited resources and a support system that may be limited as well.



And what we want to do is kind of slide the scale for the goal dependent on all of these factors being taken into consideration in a patient-centric way.

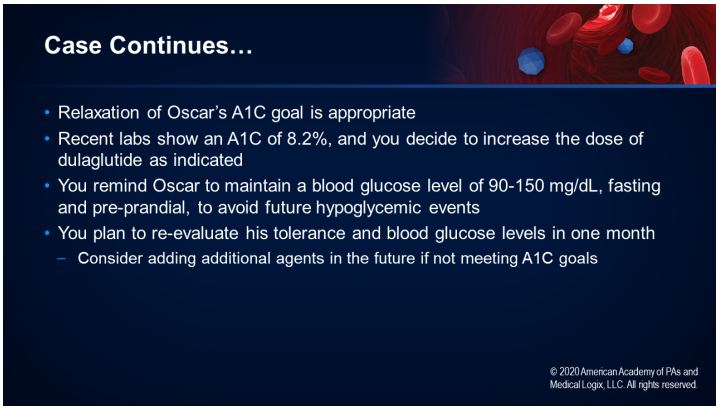
We have a U-shaped curve associated with A1C levels and the risk of mortality and cardiac events, the lowest all-cause mortality in those with A1Cs of 7.5%. Intensive glycemic control has not shown a significant reduction in cardiovascular disease outcome in large clinical trials, and we can go back all the way to the ACCORD trial, the ADVANCE trial, VADT trials. In this patient, a temporary relaxation of his A1C goal would be appropriate.



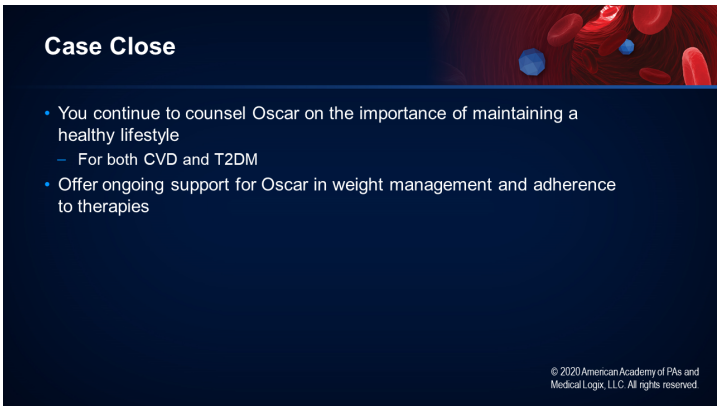
Melissa Murfin: Returning to our clinical question, relaxation of the A1C goal to less than 8% is appropriate for Oscar given his recent ischemic stroke and other clinical characteristics, making the correct (D).

Recent labs show an A1C of 8.2%, an improvement from the last reading, and you decide to increase the dose of dulaglutide as indicated in the labeling. You remind Oscar to maintain a blood glucose level of 90 to 150 mg/dl, fasting and pre-prandial, to avoid future hypoglycemic events.

After increasing the dose of dulaglutide, you plan to reevaluate his tolerance and blood glucose levels again in 1 month and add additional agents if still not meeting A1C goals.



Lawrence Herman: As we close this case, you continue to counsel Oscar on the importance of maintaining a healthy lifestyle for the management of both type 2 diabetes and his cardiovascular disease. Weight management will be an important component of this moving forward, as is adherence to the recommended therapies.



I would like to thank our expert, PA Melissa Murfin, for your great insights and discussion, and I would like to thank you, our audience, for participating in this video *eCase Challenge*.

CLINICAL PEARL

We hope you have enjoyed this *eCase Challenge* and that you have increased your knowledge and confidence in the diagnosis and management of type 2 diabetes in special patient populations.

PAs should remember that hypoglycemia is a common event in patients with type 2 diabetes and remains the major limiting factor in optimal glycemic management. Importantly, PAs should ask patients at risk about any symptomatic and asymptomatic hypoglycemia at every visit.

Patients diagnosed with type 2 diabetes often have multiple and significant comorbidities, including cardiovascular disease. PAs should review the patient history and remain cognizant of comorbidities when deciding on a therapeutic regimen and A1C goals.

Recent clinical trials of agents within the GLP-1 RA and SGLT-2 inhibitor classes have demonstrated cardiovascular benefit for multiple agents, and agents with proven benefit are recommended for patients at high risk or with established atherosclerotic cardiovascular disease.

Given the cardiovascular benefit of some agents, PAs should include these agents when appropriate to improve cardiovascular outcomes and reduce major cardiovascular events that contribute to mortality and morbidity in this patient population. Thank you again for your participation in this *eCase Challenge*.

References:

American Diabetes Association. Standards of Medical Care in Diabetes – 2020. Diabetes Care. 2020;43(Suppl 1):S1-S212.

Canagliflozin [Package Insert]. Janssen Pharmaceuticals; Titusville, NJ. 2020.

Cannon C, McGuire D, Cherney D, et al. Results of the eValuation of ERTugliflozin Efficacy and Safety CardioVascular Outcomes Trial (VERTIS CV). Presented at: 80th American Diabetes Association Scientific Sessions; June 16, 2020.

Das SR, Everett BM, Birtcher KK, et al. 2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2018;72(24):3200-3223.

Dapagliflozin [Package Insert]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2020.

Dulaglutide [Package Insert]. Indianapolis, IN: Eli Lilly and Company; 2020.

Empagliflozin [Package Insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2020.

Ertugliflozin [Package Insert]. Whitehouse Station, NJ: Merck & Co., Inc; 2020.

Garber AJ, Handelsman Y, Grunberger G, et al. Consensus Statement by The American Association Of Clinical Endocrinologists and American College of Endocrinology on The Comprehensive Type 2 Diabetes Management Algorithm – 2020 Executive Summary. Endocr Pract. 2020;26(1):107-139.

Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121–130.

Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381(9):841–851.

Liraglutide [Package Insert]. Plainsboro, NJ: Novo Nordisk; 2019.

Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–1844.

Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–322.

Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol. 2019;7(8):606–617.

Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295-2306.

Semaglutide (Subcutaneous Formulation) [Package Insert]. Plainsboro, NJ: Novo Nordisk; 2020.

Unger J. Uncovering undetected hypoglycemic events. Diabetes Metab Syndr Obes Targets Ther. 2012;5:57-74.

Yun J-S and Ko S-H. Risk Factors and Adverse Outcomes of Severe Hypoglycemia in Type 2 Diabetes Mellitus. Diabetes Metab J. 2016;40:423-432.

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-2128.Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int.* 2014;25(10):2359-2381.

CME POST-TEST: Participants must: 1) read the educational objectives and faculty disclosures; 2) study the educational materials; 3) complete the post assessments in Learning Central. See page 2 for further information.

Question #1

Which of the following factors is NOT associated with an increased risk of hypoglycemia?

A. Antecedent hypoglycemia
B. Chronic kidney disease
C. Cognitive dysfunction
D. Young age

Question #2

Which of the following statements is TRUE regarding hypoglycemia?

A. A more stringent A1C goal (<6.5%) is appropriate for patients with a history of hypoglycemia
B. Hypoglycemia only occurs in patients with T1DM
C. Hypoglycemic events can usually be identified with more frequent blood glucose monitoring
D. Previous episodes of hypoglycemia decrease the risk of a severe hypoglycemic event

Question #3

Which of the following therapies would be recommended for a patient at risk for hypoglycemia and with comorbid chronic kidney disease?

A. Dipeptidyl peptidase-4 (DPP-4) inhibitor
B. Glucagon-like peptide-1 receptor agonist (GLP-1 RA)
C. Sodium-glucose co-transporter 2 (SGLT-2) inhibitor
D. Thiazolidinedione

Question #4

Which of the following agents demonstrated a 39% risk reduction in the renal composite outcome in the DECLARE-TIMI 58 trial?

A. Canagliflozin
B. Dapagliflozin
C. Empagliflozin
D. Ertugliflozin

Question #5

Which of the following strategies would NOT help to reduce the risk of hypoglycemia?

A. Counting carbohydrates
B. Keeping a detailed blood glucose log
C. Maintaining regular mealtimes
D. Treatment intensification

Question #6

Which of the following circumstances would indicate that a loosening of A1C goals is appropriate?

A. Advanced macrovascular complications
B. Long life expectancy
C. Short duration of diabetes
D. Strong capacity for self-care

Question #7

Which of the following therapies is associated with the highest risk of hypoglycemia?

A. Dipeptidyl peptidase-4 (DPP-4) inhibitor
B. Glucagon-like peptide-1 receptor agonist (GLP-1 RA)
C. Sodium-glucose co-transporter 2 (SGLT-2) inhibitor
D. Sulfonylurea

Question #8

Which of the following therapies would be recommended for a patient with a history of heart failure?

A. Dipeptidyl peptidase-4 (DPP-4) inhibitor
B. Glucagon-like peptide-1 receptor agonist (GLP-1 RA)
C. Sodium-glucose co-transporter 2 (SGLT-2) inhibitor
D. Sulfonylurea

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- *Go with Your Gut: Improving Screening, Diagnosis, and Therapeutic Management of Patients with IBS*
- *Strategies to Address Opioid-Induced Constipation*
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- *A Call To Action: The Role of the PA in Improving Outcomes for Patients with Heart Failure*
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