Pharmacologic Approaches to Type 2 Diabetes- 2021

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T2DM - Vincent/Tsimikas

ATHENA PHILIS-TSIMIKAS, MD: Hi. Welcome to this course on pharmacologic and digital approaches to type 2 diabetes. I am doctor Athena Philis-Tsimikas with the Scripps Whittier Diabetes Institute, and here with me today, I'm joined also by my colleague Dr. Lauren Vincent who is also part of the Scripps Whittier Diabetes Institute, and the Scripps Clinic Medical Group. Lauren, glad to have you with us today.

LAUREN VINCENT, MD: Absolutely. Happy to be here.

DR. PHILIS-TSIMIKAS: Today we're going to be talking about a few topics that are incredibly important to the management of type 2 diabetes. Shown on the next slide here, you'll see the topics we'll be talking about. We're going to review the diabetes goals of therapy and glycemic targets, discuss efficacy and safety of medication classes for type 2 diabetes, review the guidelines for a stepwise approach to the pharmaceutical management of type 2 diabetes.

Lauren is also going to help you understand how to select therapy for patients with type 2 diabetes and comorbidities such as atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease, areas that have become very important in the last few years with a large number of the trials that are being conducted and have been completed.

We'll also provide you case examples of use in under-resourced populations in terms of access and implementation. And then finally, we'll finish off with some descriptions of technology that are currently offered in the ambulatory and the hospital setting for the management of type 2 diabetes.

So, with that, I'm going to start off and kick off with just a preview of the diabetes goals of therapy and glycemic targets, looking really at what the ADA has set as the standards of care most recently in 2021 in expectations really globally as well as once we dive into the pharmaceutical therapy, I'm going to turn it over to Lauren to pick that up.

Review diabetes goals of therapy and glycemic targets

So, diabetes goals of therapy and glycemic targets. If you look at what the goals of therapy are, what are the biggest challenges that we see in taking care of people with type 2 diabetes? I have to say that unfortunately these challenges have existed for quite a period of time. We have some great therapeutic approaches. We have education that's been done that can help overcome some of these challenges, yet many of these still remain. So, I think we do have to make an effort in overcoming these and addressing these individually.

So, treatment complexity; we know that the current recommendations for diabetes care can be numerous and can be complex. We know that over time there is beta cell failure, and even with the addition of medications you still might need additional therapeutic approaches in order to maintain glycemic control. Amongst this there's managing food and weight gain. So, what are our approaches that can minimize weight gain? And that's a little bit of what you'll hear about over the next hour and a half or so.

Inflexible regimens have been a challenge. Asking patients to take injections at exactly before meals or daily, or taking medications and testing blood sugars multiple times a day can all be difficult. So, how can that be addressed? Clinical inertia is a little bit on our half, the physician and provider side, and how do we keep moving on therapies? We might make recommendations but halt at a certain point. We'd like to make sure that patients are being seen on a regular basis, evaluated, and progressed in their therapy.

Then finally, avoiding hypoglycemia. We know that this also can be a challenge for patients, and also a fear that if they have an episode of hypoglycemia they might be afraid to then take on and push forward with other types of therapy. So, if we can avoid hypoglycemia in any way, that would be a benefit to the patients, and to our methods of care. So, you'll be hearing much more about all these areas over the next hour and a half.

This is the recommended approach from the American Diabetes Association on a decision cycle that includes patient-centered glycemic management. You can see in the center of this the goals of care, preventing complications, obviously, and optimizing quality of life. They start usually in the upper right-hand corner there to consider factors that impact the choice of treatment. So, we've always said for a long time you want to look at the whole picture of the patient. What do they have going in on terms of comorbidities? You want to then individualize their A1C based on this. You want to look at whether their targets should be based on do they need to lose weight, do they want to avoid hypoglycemia and avoid other side effects.

Working on down, shared decision making, ensuring that the patient is included in those recommendations and the discussion around what is the best choice for the patient. Goal setting, and then also ensuring that they get referred to diabetes education as part of their program.

Agreeing on the management, setting some goals, smart goals in particular that can be done both with the provider as well as during their diabetes self-management education program; that is a standard component in all DSME programs. Implement that plan, as we're moving now to the next area, and maintain that follow up. That's where we want to avoid that clinical inertia.

We want to make sure they're coming back, have a method and a plan in place for checking in on the patients, checking in on their A1Cs, checking in on their self-management blood glucose monitoring. Have ongoing monitoring and support, review and agree on that management plan, and then back again to the beginning where you're assessing their key patients characteristics and how are they doing on everything. So, that's your cycle, and it continues throughout the patient's lifetime.

What are a few of the standards of care that have been put in place? I won't go over all of them. There really are a whole host every year the American Diabetes Association sets forth what their latest recommendations are, but really just a few of the basic management components that have been set out. I'll go over general components and then turn it over to Dr. Vincent to give you the pharmaceutical recommendations which are really the latest for 2021.

So, in terms of weight loss, there have been recommendations, at least 5% and ideally 7% weight loss should be prescribed, recommended for patients, so that they can understand this really can make a difference in achieving their goals. But they have to be in the right mindset, so those are who are ready

to achieve weight loss. The BMI is recommended to be calculated annually when they come in and get seen.

A newer recommendation is really we are not prescribing a diet for patients with diabetes. They really can look at any of the types of diets, whether it can be Mediterranean, it can be low-fat, it can be low-carb. Any of these can work as long as there's calorie restriction associated with it. But it's part of that shared decision making where you're speaking with the patient to identify really what is the best approach to weight loss that will work for them and is preferable to them.

The physical activity recommendations remain the same, 150 minutes per week, at least over three days per week, but again, they can individualize their approach to this. No more than two consecutive days without exercise, and they've added resistance training two times a week unless it's contraindicated for any reason, and limiting sedentary time spent. Get up and move every 30 minutes. If you're wearing your Apple watch it'll remind you to do that.

Over the last few years they have also added psychosocial recommendations. So, this is important, and if there are ways for you to add the diabetes stress scale as a screening tool, that's recommended. This is only a two-question survey which can be done as a screener.

If patients test positive on this then you would go ahead and give the more extensive screener, and then if that turns our positive, a referral, an appropriate referral to resources to help address this. It's becoming more and more clear that if you don't address diabetes distress you may not be able to go on and address their other glucose management issues. So, this really does work hand-in-hand, and a partnership with the person that's helping you with this is critical.

Also maintained in this year's physician statement is the goal of individualizing someone's A1C. This has been in the recommendations for many years, and this little image on the right-hand side shows you the areas that are modifiable, at the bottom there, the last two, or not modifiable, such as what someone's age is, the diabetes duration, their life expectancy, other comorbidities. What is modifiable is the patient preference and some of their resources and support system. Really, what this would like to demonstrate is that whether they're modifiable or not, this is what you're going to be able to use in order to set an A1C target for the patient.

So, based, let's say, on comorbidities, if they're extensive, if they're older age, you many not want a really tight A1C, whereas if they've got a long life expectancy and would like to have very tight control, then you can set that lower A1C. You can see what the recommendations are for glucose goals, premeal 80 to less than 130 post meal. And this is usually by one hour, one to two hours post meal, less than 180, and then bedtime, HS, 100 to 140.

Looking at individualization of targets, we already spoke about younger and healthier. You might want to have that tighter target even as low as 6 to 6.5, but for older, multiple comorbidities, if they're more prone to hypoglycemia you might want to have that higher target, 7.5 to 8%.

All right. We also have newer ways of measuring glucose, and recommendations have been made around these kinds of targets. So, those newer ways include continuous glucose monitoring, an incredibly useful tool for looking continuously at blood sugars. It allows you to look at the blood sugars overnight. Are you having any hypoglycemia or hyperglycemia overnight? It also allows you to capture what's happening post-prandially, after a meal, and those are times when traditionally in type 2 diabetes

people aren't necessarily testing. They might have limited number of strips and aren't seeing some of these values.

So, continuous glucose monitoring can be offered intermittently in office. Even if they can't have a prescription for use all the time, you could at least get a tracing before you initiate therapy, you would get it during therapy, and then maybe a time period two, three months after therapy to see what the changes look like, and if any further recommendations are needed.

This is valuable, and the way you look at this, this the summary ambulatory glucose profile, and it tells you what is their glucose average and time in range over the entire 24-hour time period, and then also it can be over a two-week time period, or a 30-day time period; whatever you'd like to set to see what percent of the time are they within target.

This target can be adjusted, but general recommendations are 72 to 180 mg/dL is considered in target, and it's recommended that greater than 70% of the time is ideal. There also are times below target, below 70, as well as below 54, and you can see here at the bottom in red, below 70 should be less than 4% of the time, and below 54 should be less than 1% of the time. Ideally you want no values below 54, and adjusting your therapy to help avoid that is important. Time above range can also be seen, and this is time above 180, or above 250, and recommendations here are for above 180 less than 25% of the time, and above 250 less than 5% of the time.

So, very valuable in terms of use of your medications and whether those medications are working. It's also valuable for behavioral feedback. If patients are eating and are noticing that their blood sugars are rising above those goals that I showed you earlier, goal of 180 by one to two hours after your meal, they can be counseled on what kind of changes could be made within their diet in order to avoid that rise. Or adding exercise in order to help moderate the post-prandial rise, as well.

So, all those are things that can be added in addition, the things that I spoke about earlier on are important, and can help influence whether you can improve these outcomes on your ambulatory glucose profile and CGM monitoring.

So, with that, I am going to turn it over to my colleague Lauren Vincent, and she's going to take you through the efficacy and safety of medication classes for type 2 diabetes, as well as some examples of how to best use these. So, Lauren, I'm going to turn it over to you.

Discuss efficacy and safety of medication classes for type 2 diabetes

DR. VINCENT: Thank you so much, Dr. Tsimikas. I'll be taking us through some of the next sections of this course. Specifically, next I'll be discussing the efficacy and safety of our medication options for type 2 diabetes.

So, there are multiple pathophysiologic defects in type 2 diabetes. In addition to the insulin resistance that's seen at the level of the muscle and the liver, there's also decreased insulin secretion due to beta cell failure within the pancreas, as well as increased glycolysis within fat cells, decrease incretin effects within the GI tract, also increased glucose reabsorption at the level of the kidney, includes glucagon secretion at the level of the alpha cell, and finally brain neurotransmitter dysfunction.

So, really it goes without saying that our pharmacologic approach to type 2 diabetes, in order to be successful, needs to take this multifaceted approach into account with multiple drugs and multiple drug targets, if we are to achieve control for type 2 diabetes.

So, I'll be taking us through each medication class for type 2 diabetes one at a time, and highlighting some of the important factors to consider when using each medication class. I'll be starting up at the top with metformin. Metformin works by suppressing hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

It's efficacy is high, specifically A1C reduction that can be expected when using maximum dose metformin is 1-2%. Metformin is not associated with hypoglycemia, and is neutral with regards to weight change. Slight potential for modest loss, but in general really a neutral medication in terms of weight.

With regards to its cardiovascular effects, there's potential benefit with regards to atherosclerotic cardiovascular disease, and with regards to heart failure it's neutral. Its cost is low. It's oral, and with regards to its renal effects, it's neutral for the progression of diabetic kidney disease. It must be taken into account a patient's estimated glomerular filtration rate when using this medication, and I'll be going into that on the next slide.

But specifically, it's contraindicated in patients with a GFR less than 30, and additional considerations when issuing metformin are that it is associated with gastrointestinal side effects, and these are quite common. Specifically, diarrhea and nausea. There is also a potential for B12 deficiency, so some suggest monitoring B12 periodically to make sure that this doesn't develop, especially in patients who've been on metformin for some time.

So, with regards to the specific GFR cutoffs, patients who have a GFR greater than or equal to 60 can continue metformin without any dose modification. Patients whose GFR is less than 60, down to greater than or equal to 45 can continue use, but it is recommended that monitoring of renal function occurs more frequently, such as every three to six months.

Then once patients progress and have a GFR less than 45 to greater than or equal to 30, it's recommended that if a patient is not already on metformin that it be prescribed with caution, and in patients who are already on metformin, it can be continued but at a lower maximum dose, specifically half of the maximum daily dose, or 1,000 mg daily. Then when the GFR is less than 30, again, metformin should be stopped because its use is contraindicated.

Moving on to the next class is sulfonylureas. These increase endogenous insulin secretion from pancreatic beta cells, and the second generation sulfonylureas, which are those currently in use, are glyburide, glipizide, and glimepiride.

The efficacy of the second generation sulfonylureas is also high, and A1C reduction of 1-2% can be expected with this medication class. Of note, they are associated with hypoglycemia. As expected, based on their mechanism of action, they're also associated with weight gain, an important consideration when starting this medication. With regards to cardiovascular effects, they are neutral for both atherosclerotic cardiovascular disease and heart failure, and their cost is low.

They are oral, and with regards to progression of diabetic kidney disease, neutral. For dosing and use considerations in patients with kidney disease, glyburide is really not recommended, and for glipizide and glimepiride they should be initiated conservatively to avoid hypoglycemia. Then finally, there is an FDA special warning on increased risk of cardiovascular mortality, but this was based on older studies with first generation sulfonylureas, specifically with tolbutamide.

We'll be moving on to our third medication class for type 2 diabetes, specifically the thiazolidinediones or TZDs. They work by decreasing insulin resistance in the muscle, liver, and adipose cells by activating nuclear receptors, specifically the PPARγ receptors, and those are pioglitazone and rosiglitazone.

The A1C reduction that can be expected with this class is also high. The specific reduction is about 1.5%. The TZDs are not associated with hypoglycemia, but they are associated with weight gain. For the cardiovascular effects, pioglitazone may have a potential benefit for atherosclerotic cardiovascular disease, specifically stroke, but unfortunately both pioglitazone and rosiglitazone are associated with an increased risk for heart failure. Their cost is low and they are oral.

They are neutral with regards to progression of diabetic kidney disease, and no dose adjustment is specifically required when using these medications in patients with kidney disease, however, cautions should be used because of the potential for fluid retention, which of course there's a greater potential for fluid retention in patients with renal impairment, so using this medication class could exacerbate that.

Finally, there is an FDA black box warning for congestive heart failure, as already mentioned, both TZDs do increase the risk of heart failure, worsening heart failure outcomes, so they should not generally be used in patients with heart failure. They do have a potential benefit in patients with NASH.

There is, unfortunately, a potential increased risk for bone fractures with these medications, so they're generally not recommended to be used in patients with osteoporosis, and they're also, specifically with pioglitazone, may be at increased risk for bladder cancer. Finally, rosiglitazone also increases the LDL cholesterol, so some important considerations to take into account when considering using this medication class.

We'll be moving on now to some of our newer medication classes for type 2 diabetes, starting with the SGLT-2 inhibitors. So, the SGLT-2 inhibitors work by blocking the SGLT-2 co-transporter located in the proximal tubule of the kidney. So, generally when glucose is moving through the nephron, 90% of it is reabsorbed by the SGLT-2 co-transporter. So, by blocking that, a large amount of glucose remains within the nephron, and then is excreted into the urine, so glucose is removed from the body by that means.

Those currently available are canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. I listed the doses that are available for each of them, and I think it's important to mention that it's recommended for all of them to start at the lower dose, and then if A1C goal is not achieved, then to increase to the higher dose, as long as there's no contraindications such as decreased renal function.

The efficacy of the SGLT-2 inhibitors is intermediate. An A1C reduction of 0.6-1.0% can be expected when using this medication class. They are not specifically associated with hypoglycemia, however, if used in conjunction with medications that can cause hypoglycemia, such as a sulfonylurea or

insulin, it should be taken into account and potentially decreasing the dose of the medication that can cause hypoglycemia.

For weight effects, the SGLT-2 inhibitors are associated with weight loss, and specifically it seems to be related to the mechanism of action, so more fluid weight loss through the urine. For cardiovascular effects, really important to point out that for atherosclerotic cardiovascular disease, for both canagliflozin and empagliflozin there's clear evidence that I'll be getting into later that there is a benefit to using these medications.

Then for heart failure, canagliflozin, empagliflozin, and dapagliflozin all have a benefit in terms of heart failure outcomes. Their cost is unfortunately high, but luckily, and I'll also be getting into this later in the talk, there are means that we have to allow even patients who may have cost considerations as an important factor can still have access to these medications.

SGLT-2 inhibitors are oral, and in terms of diabetic kidney disease, canagliflozin, empagliflozin, and dapagliflozin all have been shown to have benefit when used again in terms of progression of diabetic kidney disease, and we'll be getting into those studies later, as well.

When using these medications in patients who have chronic kidney disease, renal dose adjuvant is required for all four of the medications in this class, specifically the GFR cutoffs vary depending upon the medication, and even the region in which they're being used. So, the manufacturing labels should be referenced to determine the GFR cutoffs for starting and using each medication.

Some important considerations: there is an increased risk for DKA, specifically euglycemic DKA with this medication class. So, these meds should be discontinued before any scheduled surgery to avoid that potential risk, usually three days before is sufficient. There's also an increased risk of bone fractures specifically seen with canagliflozin.

All of the medications in this class are associated with an increased risk for genitourinary infections and Fournier's gangrene, again explained by its mechanism of action. So, that does need to be discussed with the patients when starting these medications. There's a risk for volume depletion and hypotension, and also an increased risk for LDL cholesterol.

I'd also like to mention that there previously was an FDA black box warning for risk of amputation with canagliflozin, but within the past year that black box warning has actually been removed, and that's why I've put a strikethrough on that section here. But I do think it's still important to consider, because it does seem that there still may be an increased risk, however, the FDA has determined that it doesn't seem to be a great enough risk that the black box warning needs to remain in place.

Now we'll be moving on to the DPP-4 inhibitors, as well as the GLP-1 receptor agonists. So, these medications are incretins, and we'll be getting into their mechanism of action on the next slide. I've included here a picture of the Gila monster because the saliva of the Gila monster actually contains what's called exendin-4, and that's a structural analog of human GLP-1. It actually has a much longer half-life in the Gila monster, and so the synthetic preparation of exendin-4 was exenatide, which is suitable for human use and effectively lowers blood sugar.

So, when we eat food the active incretins in GLP-1 and GIP are released, and their levels increase in response to a meal, but their half-lives are quite short. GLP-1 is only two minutes and GIP is only five minutes.

So, their action on the pancreas is that they increase glucose-dependent insulin release from the beta cells, and decrease glucose-dependent glucagon release, and the net effect of that is that glucose uptake is increased in the peripheral tissue, and hepatic glucose production is decreased, and that results in lowering of blood sugar in both the fasting and post-prandial states.

The DPP-4 enzyme, the endogenous DPP-4 enzyme breaks down GLP-1 in GIP into their inactive forms, and so that's one of the reasons that the half-life is so short.

So, one could imagine that blocking the DPP-4 enzyme or directly stimulating the incretin receptors would have a benefit in terms of lowering blood sugar, and that is the case. So, the DPP-4 inhibitors increase endogenous GLP-1 by about two-fold, but the GLP-1 receptor analogs that directly stimulate the receptors actually increase GLP-1 levels 6- to 10-fold, and so that helps to explain why, in general, the GLP-1s are more effective than the DPP-4 inhibitors.

So, both the GLP-1 receptor agonists and DPP-4 inhibitors suppress glucagon secretion and stimulate glucose-dependent insulin secretion, but the GLP-1 receptor agonists have additional affects, again explaining their improved efficacy compared to the DPP-4 inhibitors. Specifically, they act directly on the brain to decrease food intake and decrease appetite. They slow gastric emptying and also improve first phase insulin response.

So, first I'll be covering the DPP-4 inhibitors, and then moving on the GLP-1 receptor agonists. So, sitagliptin, saxagliptin, linagliptin, and alogliptin are the four DPP-4 inhibitors that are available currently in the United States. They have intermediate efficacy, specifically an A1C reduction of 0.6-0.8% can be expected for this medication class.

They are not associated with hypoglycemia, and neutral with regards to weight change. They're also neutral with regards to the atherosclerotic cardiovascular disease outcomes, and saxagliptin, however, did demonstrate a potential increased risk for heart failure outcomes. The cost is high. They're oral, and neutral with regards to the progression of diabetic kidney disease. They can be used in renal impairment, and actually sitagliptin, saxagliptin, and alogliptin just need a dose reduction, but no dose adjustment is needed if using linagliptin.

Then some potential risks to consider. Pancreatitis has been reported in clinical trials with the DPP-4s, but causality has not been specifically established. So, in general, this medication class should be avoided in patients with a history of pancreatitis, and discontinued if the patient develops pancreatitis. The side effects are fairly mild. This medication class is fairly well tolerated. The most common side effects reported is joint pain.

The GLP-1 receptor agonists that we have are listed here. The first that was introduced in 2005 was exenatide twice a day, and then liraglutide, exenatide weekly. Albiglutide was introduced in 2014 but has been removed from the market for cost considerations from the company. Dulaglutide weekly then came out, lixisenatide daily, semaglutide weekly, and then now we also have an oral semaglutide available.

Their efficacy is quite high, and A1C reduction of 1.0-1.5% can be generally expected when using these medications. They are not associated with hypoglycemia. They can cause weight loss, and with regards to cardiovascular effects, just like the SGLT-2 inhibitors we have excellent and exciting data that show that there is a benefit with at least three of the medications within this class: dulaglutide, liraglutide, and semaglutide, with regards to cardiovascular outcomes.

Lixisenatide and weekly exenatide were neutral. For heart failure outcomes these medications seem to be neutral. Their cost is high. All but one are administered subcutaneously, specifically semaglutide has both a subcutaneous and oral form, but in general these medications do need to be injected subcutaneously.

Then moving onto the renal effects, with regards to progression of diabetic kidney disease, liraglutide, semaglutide, and dulaglutide seem to have a benefit on renal endpoints in cardiovascular outcomes trials that have been done, and that seems to be driven by albuminuria outcomes.

For considerations when using these medications in patients with kidney disease, exenatide and lixisenatide should be avoided when the GFR falls below 30, but actually, no dose adjustment is needed for dulaglutide, liraglutide, or semaglutide, and as with the DPP-4s can actually be used even in patients on dialysis, of course, with caution. Then caution should be taken when initiating or increasing the dose in patients with kidney disease due to the potential for dehydration given the side effects of this medication class, specifically, nausea, vomiting, and diarrhea.

Moving on to the additional considerations, there is an FDA black box for all of the medications in this class, given the risk of thyroid C-cell tumors that was seen in rodent studies; the human relevance has not been determined. Nevertheless, this is a black box warning and should be mentioned to patients when starting any of the medications within this class, and certainly if a patient has a personal or family history of medullary thyroid cancer, MEN, these medicines should not be used.

As mentioned, the GI side effects do need to be taken into account, specifically, nausea, vomiting, diarrhea. These are quite common with this medication class. Diet modifications can help such as encouraging patients to eat smaller meals, no fatty foods, and specifically with oral semaglutide, not taking it with too much water, and separate from foods and other medications. So, those modifications can help to mitigate the side effects, and the side effects do tend to get better with time.

Finally, most of the meds in this class do have a dose titration involved, again to help patients get used to the medication and limit the side effects. There are some injection site reactions that should be taken into account, especially with exenatide, there are small nodules that can develop that do resolve, but that should be brought up with patients so they know what to expect.

Just as with the DPP-4 inhibitors, pancreatitis has been reported in clinical trials, but causality not established. So, if pancreatitis is suspected these medicines should be stopped, and in patients with history of pancreatitis, these medications really should be avoided or used with extreme caution.

Although this isn't the focus of my talk, I do just want to briefly mention insulin, just to compare and contrast to the other medication classes which I've already discussed. So, for efficacy, insulin has the highest efficacy. It's unbeatable in terms of which medication is most efficacious, in terms of A1C-lowering potential. It is associated with hypoglycemia and weight gain, and neutral with regards to its cardiovascular effects, both for ASCVD and heart failure.

Human insulin has a low cost, but the analogs can be quite costly. Human insulin and analogs are subcutaneous, but there is an inhaled human insulin available called Afrezza. Insulin is neutral with regards to its effect on the progression of diabetic kidney disease, and in patients with CDK, lower insulin doses may be required, and so insulin doses may need to be decreased as patients' kidney disease progresses, because insulin is cleared by the kidney.

Additional considerations, some patients do have injection site reactions; those need to be monitored for and addressed. Then with regards to the hypoglycemia risk, all insulin can cause hypoglycemia, but it is a greater risk in patients who are using human insulin compared to the analogs.

Discuss efficacy and safety of medication classes for type 2 diabetes

DR. VINCENT: So, in the next section I'll be reviewing guidelines for the stepwise approach to the pharmaceutical management of type 2 diabetes. I'll be using the ADA 2021 Standards of Care Guidelines to explain the recommended approach, and also be covering the cardiovascular and cardiorenal outcomes trials that have come out that really lay the foundation for the most recent guidelines in terms of deciding upon the management of patients with type 2 diabetes, and comorbidities such as atherosclerotic cardiovascular disease, heart failure, or CDK.

This really echoes what Dr. Philis-Tsimikas already mentioned earlier on in the talk, but I do think it's worth noting that while we have an algorithm to guide us, really we should be taking a patient-centered approach and individualizing care when determining pharmaceutical management of type 2 diabetes. Specifically looking at a patient's individualized A1C target and glucose goals, comorbidities such as atherosclerotic cardiovascular disease, heart failure, and CKD.

We also should be taking into account the impact of each medication on hypoglycemia and weight. The side effect profile of medications, financial concerns, the complexity of a treatment regimen, and also patient's mental status, ability for self-care and home support, as well as language and cultural considerations. Finally, it comes down to a patient's preferences and goals, so again, while we have an algorithm to guide us, we really should be individualizing our approach to the management of type 2 diabetes within the framework of our algorithms.

So, this figure has been adapted from the 2021 Standards of Care from the American Diabetes Association, and we will be going through it step by step to hopefully give you framework and the generalized approach that you can take when deciding on medication options for your patients with type 2 diabetes.

So, up at the very top I'd like to point out that first-line therapy is still metformin according to the most recent ADA guidelines. It is, as mentioned, very efficacious, and still recommended as first-line therapy in patients with type 2 diabetes, in addition to lifestyle modification, of course.

What has been added in recent years is that we are now encouraged to assess for indicators of high-risk for established atherosclerotic cardiovascular disease, CKD, or heart failure, in conjunction with already having a patient on metformin, and the reason for this is that we now have very clear evidence that patients with atherosclerotic cardiovascular disease, heart failure, and/or CKD stand to benefit by using some of our newer available options for type 2 diabetes.

Because of this, it's encouraged that we consider these risk factors independently of a patient's baseline A1C, A1C target, or even whether or not they're able to use metformin. So, what that means is, even if you have a patient in your office whose A1C is at goal on metformin monotherapy, if they also have a history of atherosclerotic cardiovascular disease, heart failure, or CKD, we should be going down this left side of the algorithm to see if they stand to benefit from starting another medication that might help their blood sugars, but also help their cardiovascular heart failure or kidney disease outcomes.

So, specifically, when we're looking for indicators of high risk for atherosclerotic cardiovascular disease, we're encouraged to consider patients who are over 55 with coronary, carotid, or lower extremity artery stenosis greater than 50%, or left ventricular hypertrophy. For heart failure, we're especially encouraged to consider patients who have a left ventricular ejection fraction less than 45%, and then CKD we'll get into a moment.

So, if you have a patient with atherosclerotic cardiovascular disease or one of those high-risk indicators that I just mentioned, it is recommended to consider using either a GLP-1 receptor agonist with proven CVD benefit, or an SGLT-2 inhibitor with proven CVD benefit. Again, this is independent of their A1C or A1C target. I've listed here those specific GLP-1 receptor agonists that currently have proven CVD benefit, and those are liraglutide, semaglutide, and dulaglutide. For the SGLT-2 inhibitors that have proven CVD benefit, those are empagliflozin and canagliflozin.

If a patient has heart failure, again, particularly left ventricular ejection fraction less than 45%, it's recommended to consider using an SGLT-2 inhibitor with proven benefit in this population, and those specifically are empagliflozin, dapagliflozin, or canagliflozin.

Then if you have a patient with diabetes and chronic kidney disease, specifically if they have albuminuria, it's recommended to consider using an SGLT-2 inhibitor with primary evidence of reducing CKD progression, and to date those are canagliflozin and dapagliflozin. If for whatever reason canagliflozin and dapagliflozin are not feasible options for your patient, then you can consider using an SGLT-2 inhibitor that has evidence for reducing CKD progression in cardiovascular outcome trials.

So, these were studies that were done to look at cardiovascular outcomes, but then secondary outcomes looking at renal disease, canagliflozin, dapagliflozin, and empagliflozin all clearly seem to reduce CKD progression in these trials, and so, again, if canagliflozin or dapagliflozin is not a feasible option you can consider using empagliflozin. Then if for whatever reason an SGLT-2 inhibitor is not an option for your patient, you could consider using a GLP-1 receptor agonist with proven cardiovascular benefit such as liraglutide, semaglutide, or dulaglutide.

Now, if you have a patient with CKD, specifically a GFR less than 60, but they do not have albuminuria, then it's recommended to consider using an SGLT-2 inhibitor or a GLP-1 receptor agonist with proven CV benefit. Again, that comes from the fact that the outcomes in the renal trials seem to be driven by the albuminuria benefit. So, that's why there's this recommendation that if you have a patient with CKD but not albuminuria, you could consider using any one of these medications listed here: empagliflozin, canagliflozin, or liraglutide, semaglutide, or dulaglutide.

So, now I'll be shifting to cover some of these cardiovascular outcomes trials that have driven this paradigm shift in our management of patients with type 2 diabetes really in the last decade. So, I'd

like to give a brief historical perspective about where this even came from. Why do we do these cardiovascular outcome trials on new medications for type 2 diabetes?

So, before 2008, medications for diabetes focused on glycemic control. However, it started to emerge that some diabetes drugs seemed to lower glucose but possibly increase cardiovascular adverse events, specifically the TZDs. So, with that, the FDA issued a new mandate that new diabetes medications must not be associated with adverse cardiovascular events, and that seems reasonable.

So, the med classes that this applied to that came out after 2012 were the DPP-4 inhibitors, the SGLT-2 inhibitors, and GLP-1 receptor agonists. So, for each of the new medications that came out in those three classes, cardiovascular outcome trials were conducted to make sure, again, that the new medications in these classes met the criteria that they were not associated with adverse cardiovascular events.

So, these studies looked at three-point major adverse cardiovascular events, specifically cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction, or MI. These trials included more people with diabetes and concurrent cardiovascular disease, and what actually, impressively emerged is that not only were the medications in these classes non-inferior to placebo with regards to progression to the three-point major adverse cardiovascular events, but actually, some of the medications within these classes seemed to prevent cardiovascular outcomes.

So, this was very exciting as these studies were emerging, and now really seems to be taking for granted that we have medications for the management of type 2 diabetes which can also prevent cardiovascular and renal adverse outcomes. So, I'll be going through the studies briefly, comparing and contrasting them so that you can get a better sense of, again, the historical perspective, and also the available data with regards to these medication classes.

So, first I'll be focusing on the DPP-4 inhibitors, and I've listed here the four completed cardiovascular outcome trials. Each of them involves one of the four DPP-4 inhibitors versus placebo, and they looked at--the primary endpoint was three-point MACE in all but TECOS which looked at four-point MACE. In all four of them, they met the FDA-mandated criteria for demonstrating cardiovascular safety, as you can see here. So, that was excellent, and that's what the goal was, to make sure that these new medications for type 2 diabetes did not cause adverse cardiovascular outcomes.

I would like to point out that saxagliptin did seem to be associated with an increased risk of hospitalization for heart failure, and I mentioned that earlier, so it's something to take into account.

Within the cardiovascular outcome trials there were some prespecified kidney endpoints that were looked at. Specifically, I'd like to point out that albuminuria progression actually seemed to be improved with regards to using linagliptin in the CARMELINA trial.

Then finally, the CAROLINA trial, instead of comparing a DPP-4 inhibitor to placebo, it actually compared linagliptin to glimepiride, a sulfonylurea, looking at the primary endpoint of three-point MACE. So, here are the included--the CAROLINA trial, which again demonstrated non-inferiority of the DPP-4 inhibitor compared to sulfonylurea. As expected in the CAROLINA trial, linagliptin was associated with a lower risk of hypoglycemia compared to the sulfonylurea glimepiride.

So, to summarize the DPP-4 inhibitor cardiovascular outcomes trials, all four of the CVOTs reported showed non-inferiority of the DPP-4 inhibitor compared to placebo or sulfonylurea for the primary endpoint of three- or four-point MACE, and that was the objective, to make sure that these medications are safe with regards to cardiovascular outcomes. Other endpoints that were looked at, it is again noteworthy that saxagliptin was associated with an increased risk of heart failure hospitalization.

With regards to microvascular outcomes, CARMELINA is the only DPP-4 inhibitor trial with prespecified kidney outcomes, and showed no increased risk in the composite endpoint, but actually did show a benefit for albuminuria. Then finally, with regards to safety of these medications, there was no significant difference noted in the incidence of severe hypoglycemia between the DPP-4 inhibitors and placebo, but the risk of hypoglycemia was lower with linagliptin compared to glimepiride.

So, next I'll be moving on to the GLP-1 receptor agonist cardiovascular outcomes trials. So, three of them, specifically ELIXA which looked at lixisenatide compared to placebo, the EXSCEL trial which looked at exenatide compared to placebo, and PIONEER 6 which looked at oral semaglutide compared to placebo, all showed non-inferiority. So, these medications are safe compared to placebo with regards to cardiovascular outcomes. So, similar to the DPP-4 studies.

But what is really exciting is that some of these CVOTs actually showed a benefit with regards to cardiovascular outcomes for patients on a GLP-1 receptor agonist, specifically liraglutide, semaglutide subcutaneous, albiglutide, and also dulaglutide.

So, these studies are the basis of these shifted recommendations that for patients who even at their A1C target, we should consider adding one of these medications, again, dulaglutide, liraglutide, or semaglutide, because of the very clear data that suggest cardiovascular benefit in terms of time to three-point MACE.

This slide just summarizes what I've already mentioned, specifically that liraglutide, subcutaneous semaglutide, and also dulaglutide have a benefit in terms of progression to three-point MACE. Now I'll be spending a little bit of time on the SGLT-2 inhibitor cardiovascular outcome trials.

So, similarly when empagliflozin, canagliflozin, and dapagliflozin were looked at in terms of the time to three-point MACE, empagliflozin and canagliflozin were shown to be superior to placebo, and again that's where that recommendation comes from, that if you have a patient with a history of atherosclerotic cardiovascular disease, you should consider using either one of the three GLP-1 receptor agonists I've already mentioned, or empagliflozin or canagliflozin, again, in terms of the potential cardiovascular benefit for the patients.

Dapagliflozin was shown to be non-inferior to placebo with regards to time to three-point MACE, but it did demonstrate superiority to placebo for cardiovascular death or hospitalization for heart failure.

Then more recently, ertugliflozin was looked at in a cardiovascular outcomes trial, and it also was shown to be non-inferior to placebo. So again, the two that show superiority, empagliflozin and canagliflozin with regards to atherosclerotic cardiovascular disease outcomes.

Now we also have cardiovascular outcome trials that are focusing on heart failure, and specifically hospitalization for heart failure, or worsening heart failure as primary outcomes. Dapagliflozin and empagliflozin have shown clear benefit. Canagliflozin also has been shown to have a benefit, but not in a primary heart failure trial. It was in the cardiovascular outcome trial that I already mentioned. But still, the recommendation is that if you have a patient with heart failure, specifically left ventricular ejection fraction less than 45%, dapagliflozin, empagliflozin, or canagliflozin should be considered.

Then finally, we now also have renal outcomes trials. So, while renal outcomes are looked at as secondary endpoints in the cardiovascular outcomes trials I've already mentioned, now we have trials looking at renal endpoints as the primary outcome, so specifically CREDENCE and DAPA-CKD looked at canagliflozin and dapagliflozin, respectively, with regards to renal outcomes such as progression to end-stage renal disease, doubling of creatinine, or death from renal or cardiovascular cause for CREDENCE, and for DAPA-CKD looked at 50% decline in GFR, progression to end-stage renal disease, or cardiovascular renal death as its outcomes.

For both there was a clear, clear benefit for use of canagliflozin and dapagliflozin compared to placebo, and so that's why those two medications are recommended if you have a patient who has chronic kidney disease with albuminuria as the preferred medications to consider.

So, just coming back to the guidelines, again, as very clearly evidenced by the cardiovascular outcomes trials that we have available, if you have a patient with atherosclerotic cardiovascular disease as a comorbidity or indicators of high risk for cardiovascular disease, a GLP-1 with proven CVD benefit or an SGLT-2 with proven CVD benefit should be strongly considered independently of a patient's A1C or A1C targets. Specifically, those currently with data to support this are liraglutide, semaglutide, or dulaglutide for the GLP-1 receptor agonists, and empagliflozin and canagliflozin for the SGLT-2 inhibitors.

If you have a patient with heart failure, specifically left ventricular ejection fraction less than 45%, again, an SGLT-2 inhibitor with proven benefit in this population should be used, specifically empagliflozin, dapagliflozin, or canagliflozin.

Then finally, if you have a patient with chronic kidney disease and albuminuria, it's preferred to add on canagliflozin or dapagliflozin if possible based on the primary evidence in the cardiorenal outcome trials that is now available. But if those are not available for any reason you could consider also using canagliflozin, given the data from cardiovascular outcomes trials where renal outcomes were looked at as secondary outcomes, or if an SGLT-2 inhibitor is not feasible, consider using liraglutide, semaglutide, or dulaglutide.

Then finally, patients with CKD but not with albuminuria can consider using any one of these five medications given their proven CVD benefit and the increased risk for cardiovascular disease in patients with comorbid CKD.

Now I'll be briefly covering the other side of the algorithm. So, let's say that your patient is taking metformin, working on comprehensive lifestyle management, but does not have indicators for high-risk or established cardiovascular disease, CKD, or heart failure. Then, what next?

Now this is when we consider whether or not the patient's A1C is above their individualized target. If it is above the individualized target then we are encouraged to move further down the algorithm and consider whether there is a compelling need to minimize hypoglycemia, a compelling need to minimize weight gain or promote weight loss, or if cost is a major issue.

If there is a compelling need to minimize hypoglycemia then second-line medication should be one that is not associated with hypoglycemia, so specifically the DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, and TZDs are not associated with hypoglycemia and could be considered a second line.

If there is a compelling need to minimize weight gain or even promote weight loss, then either the GLP-1 receptor agonists or SGLT-2 inhibitors should be considered as second line, because those are the only two medication classes we have available for type 2 diabetes which are associated with weight loss as side effects.

Then if cost is a major issue, the current guidelines recommend considering either a sulfonylurea or a TZD as second line. So, that's in general, but I do in my current practice kind of challenge that approach, because we do have, and of course this is location and practice-specific, but there are ways to access some of the more expensive medications such as GLP-1 receptor agonists and SGLT-2 inhibitors for even some of our most at-risk patients for whom cost consideration is a great issue, and I'll be getting into that in a little bit in some cases shortly.

So, let's say that we have a patient before us in whom we've already applied our entire algorithm, and we're using those pharmacologic principles which I just reviewed, as well as comprehensive lifestyle management and diabetes education. If treatment goals are still not being achieved and injectable therapy seems to be needed to reduce A1C, it actually is recommended that the GLP-1 receptor agonists should be considered in most patients prior to insulin. This is a fairly recent update to the guidelines as well, so I wanted to point it out.

Now, of course, if the patient is already on a GLP-1 receptor agonist, or if a GLP-1 receptor agonist is not appropriate, then insulin should be considered. So, specific examples of where it might be more appropriate to proceed directly to insulin would be if a patient's A1C is very high, specifically above 10%, or if a patient has evidence of ongoing katabolism such as with weight loss, polyuria, polydipsia, then it would probably be appropriate to add basal insulin, either in conjunction with a GLP-1 receptor agonist or prior to.

But if those situations are not occurring, again, it is recommended to consider using a GLP-1 receptor agonist prior to insulin to see if A1C targets can be achieved without insulin therapy.

Provide case examples of uses in under-resourced populations in terms of access and implementation

DR. PHILIS-TSIMIKAS: Well, Lauren, that was amazing, a true tour de force through the management to the pharmaceutical management and approaches in type 2 diabetes, and also all the latest evidence and randomized control trials that really demonstrate the importance of some of these newer medications and protecting against both death, mortality, morbidity, and other challenges that we know have been not necessarily addressed in patients with type 2 diabetes, and these help to overcome those. So, thanks for much for that.

We are now going to turn to some cases that you have identified, and I think you are particularly adequate in sharing these cases, and the reason for that is you worked at community health centers now for several years which serve diverse racial and ethnic communities that might have challenges in obtaining some of the resources and the medications that really offer the best care for diabetes, and yet you've been able to obtain these medications and resources for them. So, I'm going to turn it back over to you to describe the cases and how you've been able to achieve the best care possible with this population.

DR. VINCENT: Thank you so much for those kind words. Yes, I'll be taking you through some real-world case examples to kind of demonstrate how I utilize these medications in the real world, and specifically how I tailor treatment, especially for patients who I care for that might otherwise not have access to medications due to insurance and cost considerations.

So, the first case is a 74-year-old female, and she has a history of type 2 diabetes. She presents for initial evaluation. She also has a history of coronary artery disease, hypertension, hyperlipidemia, and chronic kidney disease stage 3. Her current medications for diabetes are glargine, 30 units every night at bedtime. She's also using regular insulin before her three meals of the day, five units.

Then finally, she's also on linagliptin. She did take metformin before but didn't tolerate it due to gastrointestinal side effects. Her BMI is 34.6 and her last A1C was 8.8%. Her last GFR was 51, and her insurance is Medicaid, and in California where I practice it's called MediCal. So, she has Medicaid insurance.

So, going back to the guidelines, let's think about where she falls within the algorithm. So, first-line therapy is metformin, but she has already tried and not tolerated that. Independently of that, we should consider her other risk factors. So, as mentioned, she does have a history of coronary artery disease, so she would fall into this category all the way over on the left, where given her history of cardiovascular disease it would be important to consider whether or not a GLP-1 receptor agonist with proven CVD benefit, or an SGLT-2 inhibitor with proven CVD benefit could be prescribed to her.

Again, just to reiterate, those GLP-1 receptor agonists with proven benefit are liraglutide, semaglutide, and dulaglutide, and the SGLT-2 inhibitors with proven benefit are empagliflozin and canagliflozin. Now, some might proceed over here to the right-hand side of the algorithm saying she has Medicaid and we really should be considering cost as the primary issue, and then prescribing maybe a sulfonylurea or a TZD, but luckily, as mentioned, there are programs in place to allow patients even who are underinsured or uninsured access to some of these really beneficial newer medications for diabetes.

So, coming back to her case, I discuss the risks and benefits of the GLP-1 receptor agonist class, and also the SGLT-2 inhibitors, and she elected to try a GLP-1 receptor agonist. She was especially interested in the medication that would promote weight loss given her BMI, and in general the GLP-1 receptor agonists are more efficacious in terms of weight loss than the SGLT-2 inhibitors, so she decided on a GLP-1 receptor agonist.

So, as mentioned, she has Medicaid but there are certain federal assistance programs in place, specifically there's one that I utilize quite often here in California called the 340B assistance program, which I am able to utilize because I practice at a federally qualified health center. So, what is really

exciting is that I was able to recommend liraglutide to her, which is a very expensive medication, but luckily through the assistance program was offered to her at a reasonable and affordable monthly cost.

So, some considerations, again, to reiterate that I take into account when prescribing the GLP-1 receptor agonists are to assess for contraindications. So, I asked her whether or not she had a history of pancreatitis or any personal or family history of thyroid cancer, specifically medullary thyroid cancer, MEN. And she said no, and those are really the two main contraindications to using this medication class. I also was very careful to review the side effects, especially given her age. She's at risk for dehydration, especially if she were to develop vomiting or diarrhea.

So, as I mentioned previously, the side effects of nausea, vomiting, and diarrhea are very common with this medication class but can be mitigated by some dietary modifications such as eating smaller meals, limiting fatty foods, and also making sure to not drink large volumes of liquids with meals.

So, I make sure to review those side effects in advance so that patients can anticipate that, and also let her know that we would be starting at the lowest dose to help her get used to the medication, and that we would increase as tolerated. Side effects do tend to improve with time, and that can help patients to have that hope that if they can push through for a month or so that their side effects might improve and they'll be able to continue the medication with minimal or no side effects.

So, as mentioned, for liraglutide and other medications within the GLP-1 receptor agonist class, we start at a low dose and then gradually increase, so specifically for liraglutide the dose is 0.6 mg once a day, and that usually is continued for a week, and then the dose is increased to 1.2 daily, and then 1.8 mg daily thereafter, if tolerated, and if needed to achieve blood sugar goals. So, I always review those up titration instructions with patients but let them know that we really want them to get to the highest tolerated dose, and I'll explain more about that in a minute.

So, it's important, as mentioned, to consider decreasing insulin when starting GLP-1 receptor agonists. They are very efficacious and do not cause hypoglycemia by themselves, but other medications that might contribute to hypoglycemia if being used concurrently with GLP-1s should be decreased to minimize the risk of hypoglycemia, especially in patients who are older such as this patient who is 74.

Then finally, another consideration for when using the GLP-1 receptor agonist is their mechanism of action is redundant with the DPP-4 inhibitors, but when starting a GLP-1 receptor agonist it's recommended to stop the DPP-4 inhibitor, so I also encouraged her to stop taking her linagliptin when she started her liraglutide.

So, practical considerations are that even the patients who use insulin, I do recommend that they come in for a training session to learn how to use the specific GLP-1 receptor agonist. Each has a different mechanism and pen, and so it's important to make sure that patients understand how to use their medication properly, so I always recommend that patients bring their medication in for a training session, and if possible, administer the first dose in clinic with a certified diabetes educator, nurse, physician, PA, whoever is conducting the training sessions.

Then one more important consideration, again, just practical tips for using liraglutide, is that the pen needles need to be prescribed separately. Some such as semaglutide comes with pen needles. Trulicity, dulaglutide, doesn't need a pen needle prescription, but for liraglutide it actually is required,

and so that's an important cost consideration, especially for a patient on Medicaid. How much will the separate pen needle prescription cost, and also is that prescription active because without the pen needles they won't be able to use the medication.

So again, this is just my practical approach to starting a patient on the GLP-1 receptor agonist. Then finally, cost. So, as I mentioned, I'm able to utilize a specific drug pricing program in my practice, and for liraglutide the cost at this time is roughly $20 or $30 a month, which is a very reasonable cost for this medication class, if I'm able to utilize this drug pricing program.

So, now she comes back for follow up four months later, and so she did start her liraglutide, but she wasn't able to tolerate higher than the 0.6 mg daily dose. She did try to up it to 1.2 but really had intolerable nausea and even some vomiting. So, at our initial visit I had explained that she should try to continue her maximum tolerated dose, so when she was feeling unwell on the 1.2 mg dose, rather than stopping it entirely, she came back down to the 0.6 mg dose as directed and continued on until our follow-up visit. As directed, she also decreased her insulin, as mentioned, I recommended that to avoid hypoglycemia.

So, her glargine is currently at 23 units at bedtime. Her regular insulin, three units premeal, and she has stopped her DPP-4 inhibitor and is taking the liraglutide injection, 0.6 mg every day. On her prior medication list we have the metformin and the linagliptin, and she has lost weight. Her BMI has decreased from 34.6 to 32.5, and she's very pleased with that, and she's also pleased that her A1C has come down; now it's a 7.7%.

As mentioned, we individualized A1C targets, so in an older woman with comorbidities, 7.7 on the A1C is actually a reasonable goal, and so she's pleased to have achieved her goal A1C with the addition of this medication. So, our plan at her follow-up visit was to continue her current regimen, and we also talked about the possibility of stopping regular insulin in follow-up.

She personally wasn't quite ready to do that, and really is in her routine, but in the future will consider doing that, and that's really a success, possibly being able to stop prandial insulin in terms of hypoglycemia risk, weight gain risk, and also just injection burden.

So, that concludes the first case, and then I'd like to take us through one more case.

So, this is the case of 59-year-old female with a history of type 2 diabetes, and she also has a history of hypertension, hyperlipidemia, and diabetic kidney disease. She comes in and her current medication regimen for diabetes is detemir 22 units at bedtime, metformin 1,000 mg twice a day, and glipizide 10 mg twice a day. Her BMI is 37.8. Her last A1C was 8.9%.

Her last GFR was 47, and her urine microalbumin to creatinine ratio is greater than 300 mg/g. She also has Medicaid as her insurance. So, for her she is already on the first-line therapy of metformin, and so going down the algorithm we are assessing her for indicators of high risk for or established cardiovascular disease, kidney disease, or heart failure.

For her, she does have a history of CKD with albuminuria, so then we proceed down the algorithm and it would be preferred to use an SGLT-2 inhibitor, again with primary evidence for reducing CKD progressing if possible, and those are canagliflozin or dapagliflozin. Now, if one of those is not available,

and that does happen sometimes, insurance formularies sometimes limit and dictate which medication is preferred within each class.

So, if that were the situation, empagliflozin could also be considered, again because of its evidence in reducing CKD progression in the cardiovascular outcomes trials, and if a patient preferred not to use the SGLT-2 inhibitors, or if they were not available or contraindicated, a GLP-1 receptor agonist with proven cardiovascular benefit such as liraglutide, semaglutide, or dulaglutide could be used.

So again, with this patient I discussed her options, and specifically with her type of Medicaid she does have access to some of the SGLT-2 inhibitors with prior authorizations, so she elected to start dapagliflozin, specifically in hopes of it helping her A1C, and also protecting her kidneys.

So, my practical approach, again, would be to assess for any contraindications to an SGLT-2 inhibitor. She denied those, specifically no upcoming surgeries, and no osteoporosis. I also reviewed the potential side effects of the SGLT-2 inhibitors, specifically the risk for dehydration, genitourinary infections, just so that she could be aware of that and remember to stay well hydrated.

So, for her I also recommended reducing her insulin, again to reduce the risk of hypoglycemia when starting this medication. Again, the SGLT-2 inhibitors do not cause hypoglycemia, but they can potentiate the effects of other medications that do cause hypoglycemia such as insulin or sulfonylurea. So, I also sometimes decrease the sulfonylurea as well when starting this medication class, or a GLP-1.

Then, as mentioned, this patient's particular Medicaid insurance plan does have a formulary that includes some of the SGLT-2 inhibitors, but I always check it to see whether or not a prior authorization is needed, and for her it was needed, so I started dapagliflozin and also submitted a prior authorization to her insurance.

So, she comes back for a three-month follow up, and she has appropriately decreased her detemir as recommended down to 20 units every evening at bedtime. She continues on the same dose of metformin and glipizide, and she has started dapagliflozin 5 mg daily.

Her weight has come down a little bit, and as expected, this medication class is not as efficacious with regards to weight loss as the GLP-1 receptor agonists, however, it is important to note that it does not promote weight gain, as so many of our medications such as insulin and sulfonylurea, TZDs do. Her A1C has improved. Again, the SGLT-2 inhibitors are not as efficacious as the GLP-1 receptor agonists in terms of A1C lowering, but they do have intermediate effects, and here you can see that her A1C came down from 8.9 to 8%.

So, given that her A1C is still above her individualized target, for her a goal A1C of about 7%, we have the option of increasing her dapagliflozin to 10 mg daily. That was my recommendation, and she agreed to try it, and one consideration that needs to be taken when adjusting these medications, especially if a prior authorization was required at the initial dosing, another one, depending upon the insurance, might be needed for a dose increase, and that was the case for her. So, I submitted another prior authorization to increase the dose to 10 mg daily, and she was able to start that.

So, hopefully these two cases demonstrated how even the traditionally more costly but also more efficacious newer classes of diabetes medicines, the SGLT-2 inhibitors and the GLP-1 receptor agonists

are accessible even for our patients who are underinsured, specifically on Medicaid, depending upon regional benefits that are available.

Now I'll be turning it back over to Dr. Philis-Tsimikas to take us through the technology currently offered in the ambulatory and hospital settings for the management of type 2 diabetes.

Describe technology currently offered in the ambulatory and hospital settings for management of type 2 diabetes

DR. PHILIS-TSIMIKAS: That was terrific, Lauren. Thanks so much. We're going to take a turn now to describe some of the digital and technology components that are currently offered in both the ambulatory and hospital settings for the management of type 2 diabetes.

These digital tools have been tested in under resourced populations, but are really appropriate in almost any population. I'll first describe some digital diabetes tools that we used in the ambulatory environment, then the hospital environment, and then at the end I'll also describe how we use some of these in high-risk diabetes clinics.

In our ambulatory settings, the first tool that we developed was a digital texting tool that provided education and motivation for patients over a six-month time period. This tool was developed, though, on the backbone of one our programs that we started over 23 years ago, Project Dulce. So, I'll describe a little bit of this first and how this backbone then lead into the development of the texting tool, and the outcomes of using that texting tool.

So, Project Dulce was initiated back in 1997. It was a collaborative program together with community health centers, Public Health Department of San Diego, as well as San Diego State University. The way it works is we have a nurse-led clinical team that works together with primary care physicians in the community health centers. Added to that is a peer educator who are non-professionals that are trained to deliver classes.

These classes and team care are delivered usually in under resourced diverse ethnic and racial communities. The classes themselves are peer-led and are certified by the American Diabetes Association. Currently they're conducted as five two-hour sessions with a curriculum that's suitable across broad literacy levels, and it's been adapted for different ethnic groups as well as cultures.

This curriculum was tested in a randomized controlled trial that was supported by NIBDK, and showed that when you deliver this curriculum, compared to usual care in a community health center setting, that you can have improved hemoglobin A1C both at month 4 after baseline, as well as going out to month 10, which is 6 months after the training was completed.

So, the thought was, can we take this curriculum and somehow make it more accessible? We realized in focus groups that were done after these education classes that there are people that still have difficulty coming to classes. They're working; there's other things that interfere with their schedule. The thought was maybe if you could offer it as a texting program that you might be able to have further reach.

So, the way we developed this, we took the educational messages that were contained within the curriculum and created about 160 text messages. We then offered this in a population of Hispanic

patients, Spanish speaking and English speaking, with type 2 diabetes, with hemoglobin A1C levels over 7.5%, and randomized them once again into two groups, those that would be receiving the Dulce Digital texting program, compared to ongoing usual care within those clinics.

The endpoints, we're looking at hemoglobin A1C at 3 and 6 months. We also looked at whether the dose of the text message might make a difference in terms of that A1C outcome, as well as what was patient satisfaction with the delivery of the program.

What kinds of messages did we deliver with this? As I mentioned, there was about 160 messages delivered over a six-month time period, and there were two or three messages per day that were received, and those messages were educational or motivational. They were medication reminders, and they were also blood glucose monitoring prompts.

So the educational motivational messages that you see an example here, use small plates, portions will look larger and make you feel more satisfaction after eating. The med reminders, tick tock, remember to take your medication at the same time every day, and then the prompts for blood glucose monitoring would come in and say it's time to check the blood sugar, and then text back your results.

So, we did have then access to whether they were within range, above range, or below range. We asked them not to text back a specific number, but if they were above, below, or at target with their blood sugar values.

These blood glucose prompts report back our dashboard were then monitored on a regular basis, and the coordinator that was monitoring these blood glucose responses would reach out to the patients when certain criteria were met. So, if the blood glucose values were out of range, if one value was above 250 or below 70, so a high or low alert, that would prompt an outreach.

If they had three values that were somewhat elevated, between 181 to 250 within the month, they would have a reach-out. Or if they just weren't responding at all we would reach out again and ask if there were any barriers or challenges to obtaining their blood sugars. During the call we assess the reasons for the highs and the lows, and then we simply encouraged follow up with the primary care physician. There was no medical advice given during these calls.

So, what were the results of this study? After six months what we found was in a population that was around 48 to 50 years old, slightly more females than males, many of whom had an origin in Mexico, and preferred Spanish, and the program was offered in both Spanish and English, but the majority chose the Spanish version, with an education lower than 9th grade and with a low annual income, and a hemoglobin A1C on average of about 9.5%.

We did find that this did result in lower A1C in the group that received Dulce Digital texting compared to usual care, and this is the graph that shows the results. You see the baseline where they started, but then at month three the group in the dark boxes had a better and lower hemoglobin A1C compared to the usual care, and this was carried out and held by month six. This was a statistically significant difference between the groups.

We also looked at dose, as I had mentioned, and it turns out that those that responded more frequently to the texting about blood glucose monitoring resulted in a lower A1C as well, probably indicating that

they had more engagement with the program. We additionally did focus groups looking at satisfaction with the program, and learned that they were very satisfied with this simple program.

The conclusion we had was that the use of a simple, low-cost text messaging program resulted in greater improvement in glycemic control compared to usual care, and it was also found to be highly acceptable. I might just add the caveat that we purposefully chose a very simple texting program rather than an app, because many times people don't have a smart phone in which they can upload an app easily and have this type of communication, so we chose to have direct texting as this method.

As a follow-up to this, and over the last year and a half, as we saw that COVID was surging, we had an opportunity to apply this text messaging program in yet another way, and this was done within our hospitals with patients both with and without COVID, but that had type 2 diabetes. And we went to our hospital that was closest to the US-Mexico border, and you can see here, this is that hospital, and they also happened to have the highest rates of COVID at that time.

What we did is we brought together several programs, the first of which was the Dulce Digital texting program that we knew already was effective in terms of communicating education and motivational messages around diabetes care, but we combined it with another program that we have in the hospital.

So, we identified patients in the hospital and on discharge they received the Dulce Digital texting program, together with a transitions services program, and this program provides a health coach that will call several times upon discharge and ask are you connected to a primary care provider, do you have any questions around your diabetes, are you receiving your messages, do you have any difficulty with the texting program?

One other program that was added to this, because this was happening in the times of COVID and we had received an NIH grant to provide educational messaging around COVID awareness, misinformation, and myths, we also were able to add in some messaging around COVID in order to try and prevent greater readmission rates from COVID or diabetes complications.

So, what have we found so far with this? This once again is the description of the trial. It is a randomized controlled trial as well where half the group is receiving this texting program together with the diabetes transitions services health coach outreach calls, and we are looking at 30- and 90-day readmission rates as our primary outcomes, compared to usual care.

We're also looking at some behavioral and diabetes distress outcomes and readmission at 90 days as exploratory outcomes. So, we don't have the final yet, the study has not concluded yet, but we are able to look at whether this may have an impact. I wanted to share with you what these messages actually look like.

So, at the top here you can see, it's time to check your blood sugar. Choose where your blood sugar is. Your blood sugar--it prompts depending on what you answer back. Let's say here an E, over 250 is the result, it automatically prompts back, the blood sugar level over 250 is very high. Call your doctor if it stays high for greater than two days.

In addition to this other kinds of messaging around blood glucose monitoring, eat more vegetables. We associate a name with those. Hey, Athena, eat more vegetables. Mark on your calendar when to take

your medications. We have now also added some of the COVID messaging to look at if that might have an impact as well in terms of readmissions.

So, we'll be evaluating this over the the next year, but in addition, because we were able to restart this texting program, we've been able to offer it not only across our health system, but across California, and it is currently under evaluation with a dissemination and implementation plan that will be reaching 3,000 to 5,000 people California-wide.

We did offer this to some of our providers so that they could also see what it was like to receive these messages and be aware of what their patients are receiving, so we sent this to some of our providers down on the US-Mexico border that see patients there, and this was the response I wanted to share with you.

She sent back, "By the way, I'm actually enjoying all those great Spanish messages on not only diabetes care, but things that matter with everyday real-life events, and thinking outside the box. Well written too!" I responded, "That's great to hear, thank you." And then she responded back, "Yes!! Please send them to all my diabetes and metabolic syndrome patients. Wouldn't that be useful to start a new texting health and behavior initiative? I think patients would really think we are thinking about them and not just about their illness."

So, maybe taking as a little bit outside of the box and beyond what we usually do with care with our patients when we can offer them some of these digital tools, it may provide some other valuable means in order to help them manage their disease.

How about on the hospital side? What kind of digital interventions have become available much more recently, once again in response to COVID? I spoke earlier in the program about continuous glucose monitoring and how the American Diabetes Association is recommending that this be used in certain instances with type 2 diabetes, and because of the COVID affect and the rate in hospitals, the FDA did allow the use, it is not an approved use of devices within the hospital setting at this time, but they did allow the use during COVID in order to try and prevent and lower contact with patients that might not be needed, and also to preserve PPE.

So, we did implement this within our hospitals, and you can see that if a patient is admitted with type 2 diabetes and elevated glucose levels, continuous glucose monitoring device is placed, we then transmit the readings via a telephone that's in the room, up to a cloud. That goes then to a digital dashboard, as well as to a nursing station. The nurses are using some of the readings for treatment in addition to following and treating if there is a hypoglycemic episode, or a hyperglycemic episode that can be treated.

We additionally have a centralized diabetes advanced practice nurse that is monitoring this on a dashboard, on a central dashboard in the cloud, and looking at what the values are, and then making recommendations on a daily basis to the algorithms that might need to be adjusted in order to improve their care throughout their hospitalization.

We also have a remote 24/7 monitoring team that is looking simply at hypoglycemic episodes, so that when these patients are reaching an urgent low level they can call the bedside nurse and notify them and let them know that that patient needs treatment, to bring blood sugars back up, and avoid a severe hypoglycemic episode.

Just to share what kind of numbers we've had so far, you can see that we're treating both type 1 and type 2 diabetes, and in total to date we have reached 722 patients, of which about a quarter were COVID-positive.

So, to finish up with the digital interventions, what might be offered in high-risk diabetes clinics, and how could you use some of these digital devices to care for people in different environments? I'll just touch on how continuous glucose monitoring might be used in telehealth visits, connected pens, and hybrid closed loop pumps.

So, we know that telehealth visits rapidly increased over the last year and a half. In our setting at Scripps what we saw was video visits that went from 60 video visits a month to 3,000 a day over a three-week time period. Really rather remarkable at what we had to go through. Every time there was a surge, although the video visits dipped for a little bit, they never fell back to pre-COVID times, and would increase every time there was a surge. So, how did we use some of these digital devices in our diabetes clinics?

Again, we had spoken about continuous glucose monitoring, and we used these devices, the ones on the top here, that were placed on patients, and because all of these values can then be transmitted to a cloud, our nurses and providers that are in the clinics could then use that ambulatory glucose profile that I had spoken to you about. You can also look at daily profiles with this, in addition to this aggregate report, and look at what patients are taking, and make recommendations.

So, if their time in range is off, if their time above range or their time below range, all three are important, and you really need to use all three, you want to be preventing hypoglycemia as well as lowering hyperglycemia to make adaptations to their medical regimen.

Just to show you a little bit of how we combine this with what the patient themselves is saying, and comparing this to what we used to do, we used to have blood glucose logs and asked patients to log their own blood sugars to then also talk about what kind of food they might have been eating, if they have exercise in a day, as well as what medications they were taking that might be influencing these blood sugars.

But with the use of a continuous glucose monitor now, you can have this ambulatory glucose profile that I showed you, and along this you can train patients to say, okay, write down what medications you're taking in the morning and what doses. Write down what you might be eating, and maybe make a star where you're exercising, and they can begin to look and see, oh, I'm taking metformin 1,000 here at breakfast. Maybe they're eating cereal with milk and they're seeing those postprandial rise on average, that maybe I need to do something about that.

The same with dinner, and then also looking at overnight until the next morning. Are they coming down? Are they rising? Are they falling? So, is there an adjustment that might need to be made with their medications taken in the evening in order to optimize what their control might be. So, very valuable.

I also want to share how this device might influence behavior, personal behavior, on the part of the patient. This is one example of one of my patients who didn't quite believe that maybe his food was having so much of an influence, and he took it upon himself to do the Jujube experiment. It was his call on the Jujubes, not mine. But he was placed on a continuous glucose monitor. He had been on some

medications. And he had a box of Jujubes which he one by one, one at a time, ate those and was monitoring his CGM, and he very dramatically saw that increase, and then later on in the day the decrease.

On a telehealth visit with me, and with his wife who happens to be a lead nurse in our health system, confessed that he did this somewhat sheepishly, but really also telling us that this was enlightening to him to really see how directly the food had an impact in the rise, and at what rate that rise occurred depending on what he ate. So, very influential in terms of how these digital devices can inform patients personally of their habits.

One other comment from one of the patients that we provided a CGM to, and what her response was, she emailed back to me, and she said, "Thank you so much for arranging for me to get the CGM. It's really helping me learn how to manage my diabetes. I've been feeling sick for months, and the device and app prompted me to ask questions with my provider. I discovered that I was taking my medications incorrectly and I was causing myself to go into hypoglycemic episodes several times a day. This device literally changed my life and improved all of my symptoms just after a few days of wearing it."

So, again, very impactful in terms of how this kind of information can alter an educate someone as to how they might make changes that are beneficial.

So, if you look at some of the other devices, the CGM is great, but wouldn't it be wonderful if we could connect those CGMs to some other digital devices that we have available or are coming down the pipe.

We already have them connected to many of the pumps, and we have patients with type 2 diabetes that are insulin-dependent that may be using a pump, and the way this works, the CGM does inform the pump of highs and lows and can help adjust now the infusion rates depending on both the rate of rise and fall, as well as the absolute numbers. We've seen nice outcomes with that in terms of improving hemoglobin A1Cs and reducing hypoglycemic episodes.

The other component that would be nice if we could get this to connect a little bit more closely would be using connected pens. So, patients that maybe are not on an insulin infusion pump but are using insulin, but it's sometimes not easy to write down every time what your dose is, what time you're dosing it in relationship to the food you're eating, there are now connected pens that can begin to work and tie with the CGM so you can see all that information together and be able to advise the patient better on dosing.

So, maybe the best part of all is that this all can be done remotely just looking at the results on a report that comes via the cloud and speaking with the patient directly on a video call.

So, all of this is exciting, and offers really some new opportunities. So, I'm going to close by saying digital devices really offer a remote solution to care for management of patients, to provide individualized feedback with behavioral modification incentives, as you saw with a few of my patients, and also allows intelligent modification in pharmacotherapy.

All the pharmacotherapy that you heard from Lauren gets tied in, and you can use those now in the best way possible, based on the results you're seeing of high flows through these reports. So, lots of opportunities going forward, and I'm looking forward to all the care that we'll be able to do to optimize this for patients in the future.

I'm going to finish up with a summary, and I'm going to ask Lauren to join me on this. Maybe thinking about what are some of the summary and key takeaways from the entire program that we did, and I'm just going to bring us back to where we started, because so many of the areas that we touched upon really cover what we spoke about way at the beginning. These are the practical challenges in diabetes, and yet so many now of the options that we have can help address this.

Lauren, I don't know if you wanted to touch on any of these, and how the items that you talked about really helped you overcome some of these challenges that we have.

DR. VINCENT: Sure. So, our key takeaways are that there are certainly many medication options available for our patients with type 2, but the first consideration and most important consideration when deciding which of these medications to even use, is an individualized approach really assessing a patient's goals of therapy, and other comorbidities that might help to direct the pharmacologic approach.

DR. PHILIS-TSIMIKAS: Yeah, I think that's spot on, and a number of the approaches that you described really do help ensure that there is no deteriorating glycemic control. Many of the medications now don't cause hypoglycemia. They've simplified some of the complex treatment regimens that have been out there, and minimized weight gain.

These are all things that were touched upon in the beginning, and you really demonstrated how these new approaches can overcome this. Maybe the clinical inertia piece, from my standpoint, the digital devices that are now available can really help us overcome some of that clinical inertia because they're pushing information to us as well. We're looking at reports and saying, oh, the patient's not doing that well, we need to continue doing something.

So, we've touched on a number of things overall in the last one to two hours. We hope that you take are able to use some of these in your approaches going forward. Thank you so much for taking the time to listen to the program. Thank you, Lauren, for your input, and thank you to CMHC for everything that they are doing, as well, and communicating this information.