JOHNS HOPKINS MEDICINE
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Podcast Issue

Jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

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VOLUME 1 — ISSUE 12: TRANSCRIPT

Therapeutic Advances in Type 2 Diabetes Treatment

Our guest authors are Nestoras Mathioudakis, MD, Assistant Professor of Medicine at the Johns Hopkins University School of Medicine and Om Ganda, MD, Associate Professor of Medicine at Harvard Medical School.

After participating in this activity, the participant will demonstrate the ability to:

- Summarize the benefits of longer-acting insulin formulations.
- Discuss the safety implications of recent clinical trials with DPP-4 inhibitors.
- Summarize the glycemic and non-glycemic effects of SGLT-2 inhibitors.
- Describe the recent data on the use of SGLT-2 inhibitors in dual and triple therapy, as well as in combination with insulin.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of the management of overweight and obese patients with type 2 diabetes in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 1, Issue 11 eDiabetes Review newsletter.

Unlabeled/Unapproved Uses

Dr. Mathioudakis and Dr. Ganda have indicated that there will be references to SGLT2 inhibitors (specifically dapagliflozin) in type 1 diabetes based on the results of a randomized controlled trial by Robert Henry et al in *Diabetes Care* (2015;38:412-419)), as well as insulin formulations not currently approved in the United States: including insulin degludec, insulin degludec premixed with insulin aspart, insulin degludec in fixed dose formulation with liraglutide, and insulin glargine in fixed dose formulation with lixisenatide.

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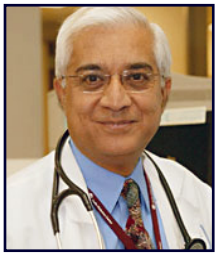

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Faculty Disclosure

Dr. Mathioudakis and Dr. Ganda have indicated that they have no financial interests or relationships with a commercial entity whose products or services are relevant to the content of their presentation.

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CME INFORMATION

⇩ PROGRAM BEGINS BELOW

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LAUNCH DATE

May 28, 2015; activities expire 2 years from the date of publication.

Length of Activity: 30 minutes

INTENDED AUDIENCE

The target audience for this initiative includes: endocrinologists, primary care clinicians, nurse practitioners, physician assistants, Certified Diabetes Educators, and other health care practitioners whose work/practice includes treating patients with T2D.

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STATEMENT OF NEED

- Clinicians do not appropriately intensify therapy as necessary to maintain glycemic control.
- Conflicting data about the safety of incretin agents may unduly deprive patients of treatment benefits.
- Clinicians are not aware of and/or are not implementing strategies to maximize the value of SMBG readings to improve patient outcomes.
- Clinicians do not adequately understand or treat to control CVD risk factors in their patients with T2D.
- Clinicians do not have a sufficiently current knowledge base to effectively consult patients about potential T2D therapeutic advances.
- Clinicians do not adequately counsel and treat their overweight/obese patients with T2D.

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• An HTML5 compliant web browser or Internet Explorer 8 (and higher)

MR. BOB BUSKER: Welcome to this *e*Diabetes Review Podcast.

Today's program is a follow-up to our newsletter on *Therapeutic Advances in Type 2 Diabetes Treatment*. With us today are that issue's authors: they're two of our *e*Diabetes Review program directors, Dr. Nestoras Mathioudakis, Assistant Professor of Medicine in the Division of Endocrinology, Diabetes, and Metabolism at the Johns Hopkins University School of Medicine in Baltimore, and Dr. Om Ganda, Associate Clinical Professor of Medicine at Harvard Medical School and a senior physician at the Joslin Diabetes Center in Boston.

*e*Diabetes Review is jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from Eli Lilly and Company, Bristol-Myers Squibb, and Novo Nordisk, Inc.

Learning objectives for this audio program include:

- Summarize the benefits of longer-acting insulin formulations.
- Discuss the safety implications of recent clinical trials with DPP-4 inhibitors.
- Summarize the glycemic and non-glycemic effects of SGLT-2 inhibitors.
- Describe the recent data on the use of SGLT-2 inhibitors in dual and triple therapy, as well as in combination with insulin.

Our guests have indicated that they have no financial interests or relationships with any commercial entity whose products or services are relevant to the content of their presentation. However, their discussion today will reference the use of SGLT-2 inhibitors in type 1 diabetes based on the results of a recent randomized controlled trial reported in *Diabetes Care,* as well as insulin formulations not currently approved in the United States: including insulin degludec, insulin degludec premixed with insulin aspart, insulin degludec in fixed dose formulation with liraglutide, and insulin glargine in fixed dose formulation with lixisenatide.

I'm Bob Busker, managing editor of *e*Diabetes Review. Dr. Mathioudakis, Dr. Ganda, thank you for joining us today.

DR. MATHIOUDAKIS: Happy to be here, Bob.

DR. GANDA: Glad to join you, Bob.

MR. BOB BUSKER: Dr. Mathioudakis, let me ask you: why are new insulin formulations needed?

DR. MATHIOUDAKIS: There are several reasons why we are constantly trying to develop better insulin formulations to mimic endogenous insulin production. We know that endogenous insulin controls blood glucose by maintaining a steady level in the fasting state and increasing in response to glucose or meals during the day and endogenous insulin does this without inducing hypoglycemia and without causing any excessive weight gain.

The problem is that the currently available insulin options do not provide a complete steady-state "peakless" action and full 24 hour coverage, and so these peaks can predispose to hypoglycemia, and weight gain, which is always a problem with exogenous insulin use. These are concerns for both patients and clinicians alike. So the goal with newer insulin formulations is to develop insulin that more closely mimics naturally produced insulin by the body.

MR. BOB BUSKER: Now I understand that these new longer-acting insulin formulations use a "depot" mechanism. Can you explain how that works?

DR. MATHIOUDAKIS: The simplest way to think about the depots is that the insulin is basically complexed in these large molecules that when you inject under the skin cause the insulin to slowly disperse more slowly into the bloodstream instead of all the insulin entering at the time of injection, so you get a longer action as a result. And that leads to a smoother and more stable pharmacokinetic and pharmacodynamic profile. In clinical practice, this mechanism could lead to fewer peaks and therefore lower risk of hypoglycemia.

MR. BOB BUSKER: Which agents using this depot mechanism are currently available?

DR. MATHIOUDAKIS: Insulin glargine U300 was recently approved in the United States, it came out in February of this year. This is a higher-strength

glargine formulation, so rather than 100 units per mL which is the exitising glargine, there's 300 units per mL so a more concentrated formulation, and this provides a longer duration of action than the U100 with a fairly similar efficacy and safety profile.

Clinical studies have found that the U300 has less body weight gain and a lower incidence of hypoglycemia, compared to the U100 glargine.

Another ultra long-acting insulin that's not yet approved in the United States is insulin degludec, this is a newer generation insulin that is available in the EU and other areas, but not yet FDA approved in the US. The degludec insulin has a half-life of more than 24 hours and a duration of action of more than 42 hours, so ultra long-acting.

In clinical trials the degludec was found to be noninferior to glargine, in terms of efficacy and had a significant reduction in nocturnal hypoglycemia, which is certainly one of the advantages of this.

And in longer term trials, in patients with advanced type 2 diabetes on basal-bolus insulin therapy, the overall rate of hypoglycemia was 24% lower and nocturnal hypoglycemia was 31% lower compared to glargine, while providing similar glycemic control.

Other trials have found that the injection time can be flexible without compromising glycemic control because of this very long duration of action.

In the real world setting, reports have found 20-30% lower doses of deguldec compared to other basal insulins to achieve the same level of glycemic control.

MR. BOB BUSKER: Have either of these insulin formulations been developed as components of premixed combinations?

DR. MATHIOUDAKIS: Insulin degludec is the first basal insulin that has been co-formulated with a rapid acting insulin analog aspart, and in Europe there is an approved combination of a premixed insulin of 70% degludec and 30% aspart that was shown to provide similar A1c reductions and hypoglycemia risk as glargine, but again only available in Europe at this time. This has the added benefit of not only targeting fasting glucose with the ultra-long acting part of the formulation, but also the postprandial hyperglycemia.

MR. BOB BUSKER: What about the use of either of these new insulin formulations in fixed-dose combinations with incretin agents?

DR. MATHIOUDAKIS: The incretin classes are really attractive options for management of prandial hyperglycemia, given its mechanism of action. There have been a lot of studies looking at combinations of basal insulin with incretin based therapy, and so the next obvious step is to combine these in fixed dose combinations, and in fact there have been several studies and one approved drug in Europe that employs this combination. The insulin is going to target the fasting glucose, the GLP-1 will target the postprandial glucose and the combination of glargine, which has a half-life of 12.5 hours and a duration of action of 24 hours, and lixisenatide, a GLP-1 agonist with a half-life of 2.6 hours, is currently under investigation in clinical studies.

In Europe the combination of insulin degludec, which has a half-life of over 24 hours and a duration of action of 42 hours, has been developed with liraglutide, the GLP-1 agonist, which has a half-life of about 13 hours, and has been approved in the European Union.

MR. BUSKER: In the newsletter issue you coauthored, doctors, you provided insight into two of the key questions our subscribers have asked us to address: the use of SGLT-2 inhibitors and the safety concerns about incretin-based therapies. Today I'd like to discuss how some of that new data can be applied in the exam room. So, if you would, Dr. Ganda, start us off with a patient situation.

DR. GANDA: This is a 49 year old patient who comes in with a history of type 2 diabetes of six years' duration. His diabetes was diagnosed at a routine physical exam. His random glucose level was 240 and A1c level was 8.5%. He's been quite conscientious about the lifestyle changes he has made, and he's been exercising three to four times weekly besides following his diet. He also has a history of hypertension and dyslipidemia. His current medications include metformin, lisinopril and hydrochlorothiazide, and atorvastatin. His home blood glucose levels have been moderately elevated fasting and clearly elevated postprandial. On physical exam, his BMI is 28.5 and his blood pressure is normal. Ankle reflexes are absent, and he has mild sensory loss in his feet. His current A1c is 7.9%, his lipid levels are good,

he has an elevated albumin-creatinine ratio of 65 mg creatinine.

After careful review of the options, the physician advised this patient to continue metformin and to add saxagliptin 5 mg daily.

MR. BUSKER: Let's first look at the major issues of concern in the management of this patient. Dr. Ganda?

DR. GANDA: This patient who has type 2 diabetes, we know he's overweight with a BMI of 28, his control of diabetes is not good, and he has significant postprandial hyperglycemia. He also has evidence of peripheral neuropathy, and we know that the severity of the hyperglycemia and duration of his diabetes are strong risk factors for retinopathy, nephropathy, and neuropathy. We also know that elevated blood sugar levels are also a risk factor for cardiovascular disease.

MR. BUSKER: Anything to add, Dr. Mathioudakis?

DR. MATHIOUDAKIS: I think the other important point to note is he had albuminuria, which we know to be an independent risk factor for CVD, and this patient had significant cardiovascular risk factors including hypertension, dyslipidemia, and albuminuria as well as uncontrolled glucose.

DR. GANDA: That's correct. In spite of his relatively short six-year duration of diabetes, he has multiple risk factors for cardiovascular disease.

MR. BUSKER: As the patient presents, he's been on metformin, and his current A1c is 7.9%. What should his glycemic goal be, and which pharmacologic options would you consider to get him there?

DR. GANDA: To prevent long-term complications, both microvascular and cardiovascular, most of us agree that the minimal goal here should be to achieve an A1c level of less than 7%. He is currently at 7.9%. We also know that after metformin, many options are now available to choose from in combination therapy: at least six quite popular options exist, including sulfonylurea, TZD, DPP-4 inhibitor, a GLP receptor agonist, or SGLT-2 inhibitor, or even insulin.

There is no firm evidence for one over the other in achieving glucose control. Often the choice depends on individual patient factors including cost, potential for hypoglycemia and weight gain, and comorbid conditions. The incretin-based agents work very well in combination with metformin without the potential of hypoglycemia and weight gain, so clearly that is one major choice. And among the incretin-based agents we have GLP-1 agonists, which are injectable; and DPP-4 inhibitors that are available orally. Several of them are currently available to choose from, and these agents are very well tolerated.

MR. BUSKER: The clinician managing this patient advised that metformin be continued, with the addition of a DPP-4 inhibitor. Dr. Mathioudakis, in the newsletter you discussed the SGLT-2 inhibitor agents. Would you consider this patient to be a candidate for one of those instead?

DR. MATHIOUDAKIS: Yes, he would be a good candidate for an SGLT-2 inhibitor for several reasons. First is his degree of hyperglycemia: his A1c is 7.9%. We know that SGLT-2 inhibitors lower the A1c about 0.7%, on par with a DPP-4 inhibitor. The other reason to consider an SGLT-2 is his weight; he's a little overweight, and these agents can help with weight loss. I think in this case the second-line choice of saxagliptin was completely appropriate. SGLT-2 would probably have a similar A1c-lowering effect.

MR. BUSKER: There have been concerns about the cardiovascular safety of incretin mimetic agents, and in the newsletter, Dr. Ganda, you described the clinical trials investigating those concerns. Would you review those for us briefly now?

DR. GANDA: The FDA has mandated that all new drugs for glucose control undergo long-term, randomized, controlled trials to establish their cardiovascular safety. Since the launch of the first GLP-1 agonist and DPP-4 inhibitor more than 8 years ago, all of these agents have been undergoing such trials, including the newer agents such as the SGLT-2 trials.

Two of the randomized, controlled trials involving alogliptin and saxagliptin have already been published. These trials included 5,300 patients after acute coronary events with alogliptin, and more than 16,000 patients with high risk for cardiovascular disease where saxagliptin was looked at. These trials lasted from 18 to 25 months, and several other trials are now nearing completion.

In both published DPP-4 trials, there was no signal for the cardiovascular adverse events; in other words, the goal that these drugs were noninferior to placebo was met. These patients, of course, were also receiving current standard of care in both groups. There were also no reports of increase in the cardiovascular disease or total mortality in these two randomized, controlled trials.

MR. BUSKER: In these trials, were there any secondary endpoints that would be of concern?

DR. GANDA: Yes. I think it's worth mentioning that in one of the randomized, controlled trials with saxagliptin vs placebo, there was a significant increase in the secondary endpoint of congestive heart failure. The hazard ratio was 1.27 with a P value that was significant. The cause is not clear. Congestive heart failure was not seen in the alogliptin trial, although there was a nonsignificant trend even in that trial. Because of this unexplained finding, other randomized control trials with other DPP4 inhibitors and those with GLP1 agonists are clearly of much anticipated interest to exactly determine whether the association with congestive heart failure that was seen with saxagliptin is really unique to that agent or it is a class-based effect.

It's worth noting that in a recent nested case controlled study from the United Kingdom there was no increase in reported congestive heart failure in a case-control analysis of several incretin mimetic agents; however, the number of cardiovascular events and congestive heart failure events in that study was relatively small, and as I mentioned, this was a case-control analysis of various incretin-based agents, not simply saxagliptin, and again, the number of cases was very small.

MR. BUSKER: Thank you both for that case and discussion. And we'll return, with Dr. Nestoras Mathioudakis and Dr. Om Ganda, in just a moment.

SUSAN PORTER: Hello. I'm Susan Porter, clinical nurse practitioner and certified diabetes educator at the Johns Hopkins University School of Medicine. I'm one of the program directors of *e*Diabetes Review.

If you found us on iTunes or on the web, please be sure to subscribe. This podcast is part of Johns Hopkins *e*Diabetes Review, a new educational program providing monthly activities certified for CME credit and nursing contact hours, with expert commentary and useful practice information for clinicians treating patients with type 2 diabetes.

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MR. BUSKER: Welcome back to this eDiabetes Review podcast. I'm Bob Busker, managing editor of the program. Our guests are Dr. Om Ganda from Harvard Medical School and Dr. Nestoras Mathioudakis from the Johns Hopkins University School of Medicine. And our topic is *Therapeutic Advances in Type 2 Diabetes Treatment*.

We've been looking at how some of the new information our guests discussed in their newsletter issue can be applied in the exam room. So to continue — if you would, Dr. Ganda — please bring us another patient scenario.

DR. GANDA: This is a 56 year old office manager who has a history of type 2 diabetes for the past several years. She presents with a specific question about her diabetes management. She had been treated with metformin since diabetes was diagnosed a few years ago. She's currently on 1,000 mg of metformin BID. Because of her ongoing inadequate control, she was started on glimepiride 2 mg daily; however, she has had several episodes of hypoglycemia at times after she delays a meal or after exercise. She often omits glimepiride when planning a busy day traveling for work, which complicates her control even further, and control remains inadequate. She was advised to stop glimepiride and just continue metformin and start sitagliptin 100 mg daily while continuing metformin.

She reads on the Internet that the incretin-based agents, including sitagliptin, have been associated with increased risk of pancreatitis and possibly pancreatic cancer, and she comes to see you for a second opinion.

MR. BUSKER: There is a lot of information on the internet — some of it fact-based, a lot of it not — about a link between incretins and pancreatic damage. What would you tell this patient?

DR. GANDA: This is a complicated question. Anecdotal cases of acute pancreatitis have been reported with both GLP-1 agonists and DPP-4

inhibitors. However, the epidemiological studies have shown that patients with type 2 diabetes have an approximately two-fold increase in risk for pancreatitis compared to people without diabetes. We also know that the risk factors of pancreatitis include obesity, gallbladder disease, alcohol excess, and very high triglycerides (above 500); and many of these risk factors are present in patients with diabetes.

This issue has also been raised by certain studies in animal models of obesity and diabetes, where agents of the incretin class were reported to cause histological changes consistent with pancreatitis, and even some premalignant changes. However, the relevance of those animal studies to humans is quite unclear.

DR. MATHIOUDAKIS: In fact, the FDA here in the US and the EMA — the European Medical Agency — have been examining large databases to see if there's any real connection between the incretin class of medications and pancreatitis or whether this is just an association. According to that report there is really no current evidence for an increased risk for pancreatitis or pancreatic cancer, but there is certainly a need to complete these ongoing studies before any definitive conclusion can be made.

MR. BUSKER: In the clinical trials that have been published, was there any data that supports an association between incretin agents and pancreatitis? Dr. Ganda?

DR. GANDA: To explore this possible association between incretin mimetic agents and pancreatitis and pancreatic cancer, in both randomized, controlled trials I mentioned that used alogliptin and saxagliptin, there was no significant increase in the rates of pancreatitis or any type of cancer. We should also point out that in the trials with large numbers of patients — in the saxagliptin trial in particular which had more than 16,000 patients — this issue was addressed in more detail in a separate publication. In that study, an equal number of pancreatitis events was seen in the group receiving saxagliptin and placebo. So one can say that thus far in these randomized control trials with two different DPP-4 agonists, there was no association with pancreatitis.

MR. BUSKER: What about pancreatic cancer?

DR. GANDA: The question pancreatic cancer is even more difficult to answer with the randomized, controlled trials so far that have only lasted up to two years. For example, in the saxagliptin trial, there was a small but nonsignificant decrease in the number of cases reported. In other words, five cases with saxagliptin and 12 cases with placebo; however, those events were just too few among the more than 16,000 patients to draw any definitive conclusions. Therefore, the results of several ongoing randomized, controlled trials with various DPP-4 inhibitors and GLP-1 agonists are eagerly awaited.

MR. BUSKER: Thank you, doctors, for clarifying what's known on the topic. I'd like to look at one more patient situation now — and let me turn to you for that, Dr. Mathioudakis.

DR. MATHIOUDAKIS: This was a 58 year old man who had type 2 diabetes for 20 years but surprisingly only had peripheral neuropathy as a complication, despite having diabetes for that long. He had a lifelong history of obesity, his maximum weight was 265 pounds before his diagnosis, and when he first saw me he had a BMI of 32 and was really concerned about his weight. He had been on three oral agents for at least the last year: metformin at maximal doses, sitagliptin 100 mg daily, and glipizide 10 mg twice daily. He was very compliant with treatment and very motivated to get his A1c to goal.

About 3 months before seeing me for the first time his A1c was 8.6% but at the time of his first visit his A1c had come down to 7.9%, just making significant dietary changes, predominantly following a lower carb diet. He did not really engage in any regular exercise. He did have a lot of cardiovascular risk factors, including obesity, hypertension, and dyslipidemia, and he was also a smoker. His blood pressure was 142/77 at his visit and he had some mild vibratory sensory loss.

So at his first visit we really talked a lot about intensifying his exercise. We provided him a prescription for a Blue StarTM program, which is a mobile prescription therapy that provides personalized guidance for people with diabetes. In addition, because his A1c was above target on three oral agents, we discussed starting canagliflozin at 100 mg daily.

MR. BUSKER: So with this patient you're considering adding an SGLT-2 inhibitor — a fourth OAD medication. What's your rationale for that, and what might some of your other options be if you didn't want to go to this quadruple therapy?

DR. MATHIOUDAKIS: As I mentioned earlier, the SGLT-2 inhibitors are mild glucose lowering agents; they drop the A1c about 0.7%. As you recall, he had an A1c of 7.9, so we were hopeful that would get him pretty close to the target A1c of less than 7%. The other main consideration in his case is that he was obese, and weight loss was a high priority, and these agents are associated with weight loss because they work by calorie loss through glucosuria.

Finally, he had some mild elevations in his systolic blood pressure, and recent clinical trials have shown favorable blood pressure effects from these agents.

MR. BUSKER: Dr. Ganda? Your thoughts?

DR. GANDA: I agree with Dr. Mathioudakis that this patient really needs further assistance with his glucose control. We definitely would like to favor drugs that improve blood pressure and achieve some weight loss. In that direction, one of the options would be to ask him to stop the DPP-4 inhibitor, and in place of that drug he should start a GLP-1 agonist, which will also have the advantage of inducing some weight loss and thereby lower the blood pressure.

DR. MATHIOUDAKIS: That was my go-to medication in his case, it was my preference that he switch the DPP-4 to a GLP-1 agonist. Unfortunately he was very averse to the idea of injectable therapy of any kind, so we thought it was reasonable to give an SGLT-2 inhibitor a try. And the other point worth mentioning to the listeners is, when someone is on three oral agents and has not achieved glycemic control, we consider moving toward basal insulin. But given his obesity and his reluctance to inject insulin, this wasn't the best option for him at this point.

MR. BUSKER: These SGLT-2 inhibitors are fairly new agents, and many of our listeners may not have much experience with them yet. Which agents are FDA approved at this point?

DR. MATHIOUDAKIS: Three SGLT-2 inhibitors are FDA-approved in the United States: canagliflozin, which comes in a 100 mg and 300 mg dose; dapagliflozin, 5 mg and 10 mg; and empagliflozin, 10 mg and 25 mg dose. All of them are dosed once daily. All of these medications are approved for use in type 2 diabetes only, although there is some emerging evidence that they can be beneficial in type 1 diabetes because they work by noninsulin-dependent mechanisms. So they could potentially lower insulin requirements, even in patients with type 1 diabetes.

MR. BUSKER: That evidence about potential efficacy in type 1 diabetes was published in *Diabetes Care*, and a link to it can be found in the transcript version of this podcast.[1] Dr. Mathioudakis, what about the contraindications to the use of SGLT-2 inhibitors?

DR. MATHIOUDAKIS: The main contraindication is renal insufficiency. These drugs all work by blocking the receptor in the kidney that is responsible for glucose reabsorption, so they cause glucose excretion in the urine, which could potentially lead to dehydration. Glomerular filtration rate < 60 is a relative contraindication for canagliflozin and dapagliflozin, and a GFR < 45 is a relative contraindication for empagliflozin. And all three of the SGLT-2 inhibitors are contraindicated for GFR < 30 or any end stage renal disease with patients on dialysis.

MR. BUSKER: These SGLT-2 agents are all approved for second- or third-line use. How safe and effective have they been found to be in combination with other glycemic control agents? What does the evidence from the recent trials tell us?

DR. MATHIOUDAKIS: The March 2015 issue of *Diabetes Care* was devoted entirely to randomized clinical trials of SGLT-2 therapy. At least 12 studies were devoted to the topic, and the SGLT-2 trials were evaluated in varying combinations with other oral agents. One of the studies that I reviewed in this newsletter that accompanies this podcast looked at canagliflozin in combination with metformin vs a sulfonylurea in combination with metformin.[2] The study showed that canagliflozin was more effective than glimepiride at 2 years with a mean A1c change of – 0.7% in the canagliflozin and – 0.055% in the glimepiride group, which was significant.

Another study reviewed in this newsletter was dapagliflozin as add-on therapy to metformin and a sulfonylurea, which is a regimen that my patient

in this case was already taking.[3] The study showed that at 24 weeks, the addition of dapagliflozin resulted in an additional A1c lowering of 0.86% compared to placebo.

And then another study that was examined was the combination of an SGLT-2 and a DPP-4 inhibitor with metformin.[4] The authors looked at dapagliflozin and saxagliptin in combination with metformin, which is relevant to the case at hand. That study found that triple combination therapy resulted in an additional lowering of the A1c of 0.6% compared to dual therapy with metformin and a DPP-4 inhibitor.

Finally, there was a clinical trial looking at the combination of SGLT-2 inhibitors in combination with insulin in type 2 diabetes.[5] And this was a study of canagliflozin in combination with insulin in patients with long-standing type 2 diabetes, many of whom have advanced complications. And the findings of the study were at one year follow-up the addition of canagliflozin to patients already on insulin and other oral agents resulted in an A1c reduction of 0.7%.

MR. BUSKER: Dr. Ganda? Anything to add?

DR. GANDA: I think it's important to emphasize in a patient who is already on insulin that many of these patients have long-standing diabetes, as Dr. Mathioudakis said, and they need insulin. But on top of insulin they can achieve better control by adding an SGLT-2 inhibitor rather than going to multiple insulin injections.

DR. MATHIOUDAKIS: That's a very good point, and there is some evidence that adding the SGLT-2 inhibitor may help reduce insulin requirements for patients, which may be beneficial from a weight standpoint.

DR. GANDA: I think for the private practitioner this is important to emphasize because, as you said, they could have increased the dose of insulin, which they didn't; but the other option would have been to add prandial insulin, should that be necessary.

MR. BUSKER: In the newsletter issue, you mentioned some of the non-glycemic benefits of SGLT-2 inhibitors. Dr. Mathioudakis, review those for us again, if you would, please.

DR. MATHIOUDAKIS: The studies collectively showed about approximately a 2 to 4 kg weight loss with SGLT-2 inhibitor therapy, and additional blood pressure reductions of about 3 to 4 mm Hg systolic, which I think makes sense given how these agents work.

MR. BUSKER: What are the main adverse effects that clinicians need to be aware of when prescribing these drugs?

DR. MATHIOUDAKIS: The most concerning and most common adverse effect is genital infections. These are typically fungal infections, for women vaginal candidiasis, and for men there can be candidal infections of the groin and penis. These studies showed about 10% of participants experienced this outcome. In addition, urinary tract infections are more common, and of course, the infections are increased because of the increased glucose in the urine and the resulting growth of the organisms.

The other concern is volume depletion, and so orthostasis in potentially elderly patients or even patients with advanced neuropathy or autonomic neuropathy, could that be an issue. It turns out that's a pretty uncommon side effect in these studies and really didn't become an issue unless patients were taking these agents in addition with insulin or taking them in combination with insulin.

Renal function was generally stable in the participants who took it and most of them had GFRs above 60, which is the indication that they're approved for. The risk of hypoglycemia is very low, but again, when these agents are given in combination with insulin therapy, there may be a slightly higher risk of hypoglycemia.

DR. GANDA: Yes, and I should add that these drugs are currently quite expensive and may not be covered by all the insurance third parties. Also, like the DPP-4 inhibitors and GLP-1 analogs for which we are awaiting other trials, we also need long-term clinical outcome trials with SGLT-2 inhibitors, particularly the cardiovascular outcome trials.

DR. MATHIOUDAKIS: Regarding the cost, if you have a patient who's on insulin and multiple oral agents and you hope to try to lower insulin requirements by adding these very expensive oral agents, it may not make sense because insulin is a lot cheaper and titrating insulin doses may be just more cost effective for a patient.

MR. BUSKER: This 58 year-old male patient you described for us — you started him on quadruple therapy by adding an SGLT-2 inhibitor. How did he respond?

DR. MATHIOUDAKIS: He came back to clinic about three months later and was really pleased that he had lost about 7 pounds, and his A1c was 6.7% at the follow-up visit. You'll recall it was 7.9% 3 months earlier, so that was a greater A1c reduction than we expected. But I think that that was more due to the combination of this medication and really intensified efforts at exercise for this patient who was previously quite sedentary. And his blood pressure was a little lower at the follow-up visit, 137/77, consistent with the effect of these medications. He had no problems with groin infections or urinary tract infections or volume depletion.

MR. BUSKER: I want to thank you, doctors, for sharing your insight and expertise through today's case scenarios. And I'd like to ask each of you to take a moment now and focus on the future for us. The SGLT-2 inhibitors, Dr. Mathioudakis — what are the questions we most need answered?

DR. MATHIOUDAKIS: The most important information we still need from this new class of medications is long-term efficacy data on clinical endpoints, cardiovascular disease, and microvascular complications. These drugs have been around now for about 3 or 4 years, so it's going to take another decade or more before we really get a clear answer about hard clinical outcomes. I think that's going to be the focus of future clinical studies for this drug class.

The other point is, some pilot data suggests that SGLT-2 inhibitors may be beneficial in type 1 diabetes. These small studies and larger studies of type 1 patients may provide important information about their role in that population. But again, I want to reiterate that SGLT-2 inhibitors are not FDA approved currently for type 1 patients.

MR. BUSKER: Dr. Ganda, the incretin based therapies. What do you expect the future holds?

DR. GANDA: Two items come to mind. First, the FDA is now reconsidering and convening to look at the entire situation with cardiovascular outcomes with incretin-based agents. One of the DPP-4 trials with saxagliptin showed a significant signal of increased rates of congestive heart failure. We are waiting to see what the other trials show, and the FDA is looking at all the data with the ongoing studies with the incretin-based agents.

The second item is that in spite of the excitement about all the new drugs we have, we still don't have a very good handle on the efficacy and durability in back-to-back comparisons or side-to-side comparisons of these various agents after metformin. NIH is conducting a randomized, controlled trial in which patients who failed metformin alone and have A1c of greater than 7.5% are being randomized to four arms which include glimepiride as the sulfonylurea, sitagliptin as the DPP-4 antagonist, and liraglutide as the GLP-1 agonist, and basal insulin. This is an important study to look at the effect of these agents on A1c reduction over time and also indirect endpoints such as beta cell function.

DR. MATHIOUDAKIS: I agree with Dr. Ganda that this NIH study will be really important and will inform the algorithms that we use in treating patients with diabetes. Unfortunately, the study was designed before SGLT-2 therapy became available, so we are not evaluating SGLT-2 therapy in this study.

MR. BUSKER: Thank you both for sharing your thoughts. I'd like to wrap things up now by reviewing the key points of today's discussion in light of our learning objectives. Dr. Mathioudakis, let me start with you and the first learning objective: summarizing the benefits of the longer-acting insulin formulations.

DR. MATHIOUDAKIS: Longer-acting insulin formulations use a depot mechanism that provides a smoother and more steady release of insulin, which has the benefits of a lowered risk of hypoglycemia, and potentially less weight gain. And one added advantage to the insulin degludec, is because it's so ultra long-acting, it can be given enough flexible dosing schedule, which is likely to improve patient adherence.

MR. BUSKER: And our second learning objective: the safety implications of the recent clinical trials with DPP-4 inhibitors, Dr. Ganda?

DR. GANDA: I would say that DPP-4 inhibitors have proved the test of time so far, and they appear to be quite safe, although there are some lingering questions about their long-term effects on pancreatitis and pancreatic cancer, which so far has not been shown in any of the randomized clinical trials. We also have to wait for other trials to establish the cardiovascular safety of these agents.

MR. BUSKER: The glycemic and nonglycemic effects of the SGLT-2 inhibitors. Dr. Mathioudakis?

DR. MATHIOUDAKIS: So the SGLT-2 inhibitors as a class have modest glucose- lowering effects of about 0.7% on the A1c, on par with DPP-4 inhibitors. They also have a favorable blood pressure effect of about 3 to 4 mm Hg and a weight loss of about 2 to 4 k.

MR. BUSKER: And the use of the SGLT-2 inhibitors in dual and triple therapy, as well as in combination with insulin.

DR. MATHIOUDAKIS: The SGLT-2 inhibitors have been tested in combination with metformin and DPP-4 inhibitors, as well as metformin/sulfonylurea therapy, and with insulin therapy in combination with oral agents. I think the take-home message from all of these trials SGLT-2 is that inhibitors cause an additional lowering of the A1c of about 0.7% regardless of how they are combined with other agents.

MR. BUSKER: Dr. Om Ganda from Harvard, Dr. Nestoras Mathioudakis from Johns Hopkins — thank you for being part of this *e*Diabetes Review Program.

DR. GANDA: Thank you very much, it was a pleasure to join you in this very important podcast.

DR. MATHIOUDAKIS: It's been really great talking with you today, Bob.

MR. BUSKER: This is Bob Busker with a brief Editor's Update. Shortly after this podcast was recorded, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee recommended that two DPP-4 inhibitor agents — saxagliptin and alogliptin — have their labels updated to include information about cardiovascular safety issues. Additional studies investigating these concerns are underway, with some results expected relatively soon. No other incretin-based agents, either DPP-4s or GLP-1s, were addressed in the Advisory Committee's recommendations.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.ediabetesreview.org/test.

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