CLINICAL COMPENDIUM

Advancing the Care of Patients With Type 2 Diabetes and Chronic Kidney Disease: Role of the Glucagon-Like Peptide-1 Receptor Agonists

Print Transcript

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Module 1: Background

George Bakris, MD: I will begin talking about type 2 diabetes and kidney disease. The number 1 cause of kidney failure in the world is diabetes. Type 2 diabetes is not going away. In the next 20 years, it's estimated to rise by 51%, reaching 700 million or 10.9% of the global population by 2045. Diabetic kidney disease is one of the most common complications arising from diabetes, and it's affecting about 40% of people with diabetes; DKD may represent, at the time of diagnosis, a presence of disease. In other words, if you have diabetic kidney disease, a lot of people don't know it, and when they're first diagnosed with diabetes, they're told they have kidney disease unbeknownst to them.

Diabetic kidney disease is defined as changes not only in function but in kidney structure. The way you define this is by knowing 2 key components, and we're going to talk more about them as we go through the talk. The 2 key components are the estimated glomerular filtration rate (GFR) and persistence of albuminuria.

Chronic hyperglycemia is the key risk factor that transforms inflammatory cells to become present and changes within the renal architecture, and ultimately, over months to years, leads to a number of changes that lead to kidney function deterioration. These are changes at the renal cell level, at the tubules, and where you have glucose toxicity. With high intracellular glucose concentrations, the cell has to adapt. It's all about adaptation, and it's not normal for cellular glucose levels to be high. Consequently, a number of things happen: advanced glycation end products develop, inflammatory cytokines increase, growth and fibrotic factors increase, and prolonged exposure of cells to these substances leads to cell death, injury and kidney failure.

I mentioned earlier, worldwide, there's an increased incidence of diabetes, but there's also an increased incidence of diabetic kidney disease leading to end-stage kidney disease (ESKD). If you see, on the left, worldwide there will be a little more than a doubling in 2030 of the number of people on dialysis from diabetes compared to 2010. You can see this is a problem primarily in Asia, but notice North America is right behind.

If you then look at the kidney as a cardiovascular risk factor, I think it's important. So, yes, you have diabetes; yes, you've developed kidney disease. What is the effect of that on mortality? That was looked at a number of years ago at the Kaiser in California where they looked at over a million people. They looked at the range of GFRs, and what you have here on the left is all-cause mortality and when the GFR goes below 45 ml/min/1.73 m^2, there's over a 4.5-fold increase in all-cause mortality. At the same level of GFR, when you come over and look at cardiovascular events, there's over an 11-fold increase. So, kidney disease is not just kidney disease. Kidney disease is a reflection of very high cardiovascular risk.

If you have kidney disease, what specific problem are you going to have? The most common cardiovascular problem that you're going to have is heart failure. If you look at this study, and look at the left side of the screen, these are people with kidney disease; 43% of the cardiovascular events are going to be related to heart failure, whereas if you look at people without kidney disease, it's only 18.5%. So, heart failure's a major issue.

Now, the American Diabetes Association and the International Kidney Guidelines have gotten together and melded the 2 guidelines that they have on diabetic kidney disease together. This is a summary of what is in the published document, and it tells you who and when to screen, how to screen. You'll notice albuminuria or spot albumin creatinine ratio; spot urine, is at the top that trumps eGFR, but it's a marriage. You need both. So, it's not 1 vs the other—you need both. You see right below it what defines a diagnosis of chronic kidney disease: persistent urine albumin of greater than or equal to 30 mg/g and/or persistent eGFR below 60 ml/min/1.73 m^2. Also, there could be other evidence of kidney damage. You need to repeat this to confirm these numbers. As I mentioned earlier, there's a modification of the current equation to assess estimated GFR; this equation is going to give an even more accurate measure of what kidney function is in the respective patients.

Now, what you see before you [2022 ADA/KDIGO CKD Staging Heat Map], you need to Xerox, you need to put in every exam room, you need to educate the nurse practitioners, the PAs and everybody in the office about this. This integrates everything that you're going to hear or most things that you're going to hear today, because it tells you, on the left, what your GFR is and what stage of kidney disease you have and, across the top, it tells you about albuminuria and what stage of albuminuria you have. When you say to somebody that you have stage 3a CKD, that only describes the GFR. You need to say if they have microalbuminuria, that they have 3a A2, or if they have more than 300 mg of albuminuria, you can say they have stage 3a A3. That needs to be communicated in the chart, but more importantly, the patient needs to see this picture. You're not going to necessarily walk them through in detail like I just did, but what you're going to to say, "Okay, based on your GFR, based on your

albuminuria, you're in this square." I will guarantee you, if the square is red, they will know they're in trouble. You don't need a big explanation. They will know they're in trouble. If it's in orange, they will know they're in trouble. And even if it's in yellow, they're going to be concerned as to what do they need to know.

This needs to be communicated to the patient because kidney disease and diabetic kidney disease are silent killers. It's a silent disease. You are asymptomatic. You don't have a clue. I have a number of patients who come into my office, and they're referred, and I have to tell them that their GFR is 30 ml/min/1,73 m^2. "What does that mean?" I tell them what it means: it's a huge problem. I show them the map, and the common question almost in everybody is, "Why wasn't I shown this by my primary care provider?"

It's important because they will listen to you. They will follow your lead if they know where they are. They're not going to feel it. They're not going to have any pain. It's important.

Module 2: Standard of Care

George Bakris, MD: Let's talk about the standard of care. Where are we with the standard of care? It's come a long way in the last 20 years. The concept that I'd like you to embrace is a concept that I utilize from the heart failure cardiologists, and that is "pillars of therapy." We now have a structure that has been erected and can be supported by different pillars of therapy. The heart failure [cardiologists] do it all the time. They have 4 different drugs that they use, and they use them all in heart failure. We now have 3 different drugs, and we should use them all, regardless of the situation. I'm going to walk you through this.

We have blockers of the renin angiotensin system (RAS); this goes back to the year 2000 and before. The maximally tolerated blockers of the renin angiotensin system, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), are key to slowing progression of diabetic kidney disease. We now have the sodium glucose cotransporter-2 (SGLT2) inhibitors, and we're going to talk a little about that. We have finerenone, a nonsteroidal mineralocorticoid receptor antagonist (MRA). This is not spironolactone; finerenone is very different in many ways, chemically and physiologically. This is solid, grade A trial data endorsed by the guidelines as therapies that must be used in people with diabetic kidney disease.

Now, taking it a step farther, you don't just put patients on the drugs. You have to follow the ADA/KDIGO combined consensus report. Lifestyle is key. First-line therapy, anybody that has diabetes, that has kidney disease and/or heart failure, must be on an SGLT2 inhibitor, period. If you want to use metformin for glucose control, that's fine, but they must be on an SGLT2 inhibitor. They must be on a RAS blocker if they have any level of albuminuria and any level of blood pressure. Finerenone should be used if they have albuminuria, even after those therapies, that's more than 30 mg/g because it's been shown to be a benefit down to a GFR of 25 ml/min/1,73 m^2. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a must if there's a history of atherosclerotic cardiovascular disease in these patients. There's data coming out on renal benefit, and I'm going to show you some of that data later, but I think it's important to understand that this is where we are now and this, with lifestyle, has shown a dramatic improvement in slowing kidney disease progression and reducing heart failure risk.

If we look at SGLT2 inhibitors—this is a meta-analysis that was done. There's 1 even more recent than this. The bottom line is that SLGT2 inhibitors have shown a benefit in terms of reducing heart failure risk in these patients. Without any question, a very important point, and there's been a benefit on cardiovascular death as well. I think one must look at these agents as not glucose-lowering agents. These are cardiorenal risk-reducing agents that happen to lower glucose with good kidney function. But if your GFR is 30-40 ml/min/1,73 m^2, they have amazing benefits on preserving kidney function, reducing heart failure risk and they don't do anything to glucose at that point.

In terms of safety issues with SGLT2 inhibitors, you have to worry about volume depletion in these patients. You don't want them volume-depleted, and the other thing is acute kidney injury. Do you have a problem with acute kidney injury? No. Do you have a problem with hyperkalemia? No. In fact, if you use these agents with finerenone, these agents will protect you from developing hyperkalemia. There's a very nice paper that was published just within the last year from the finerenone FIDELIO trial showing this. This is very important to keep in mind. A real thing is the genital mycotic infections which are significant and do happen. You have to warn the patients to keep the area very dry and 1 of the things that I encourage is a cornstarch-based baby powder that they can use there that's absorbent.

Volume depletion can occur, especially if your GFR's above 60 ml/min/1,73 m^2, and your glucose is not well controlled. For the genital mycotic infections, it doesn't matter what your GFR is, you're susceptible to those and you need to be aware. If you have a history of urinary tract infections, you can get into trouble here, but it's uncommon.

This is a very nice meta-analysis that shows you, from the clinical trials, whether you have atherosclerotic cardiovascular disease or not. The SGLT2 inhibitors protect the kidney. They reduce progression to dialysis, reduce renal death, and reduce 50% reductions in GFR. It doesn't matter what trial you look at, they're all good.

The nonsteroidal MRAs were developed because you can see from the graph on the right, we reduced residual risk with the ACEs and the ARBs, but it was still gargantuan. With the CREDENCE trial, the DAPA-CDK trial with the SGLT2 inhibitors, we further reduced residual risk, but you can see there's still a lot of residual risk.

These drugs have some hemodynamic effect, don't really have any metabolic effect, but have a very large anti-inflammatory, antifibrotic effect. When you look at the FIDELITY analysis, we designed it as 2 different trials: the FIDELIO-DKD which was a diabetic nephropathy outcome trial of over 5,700 patients and the FIGARO-DKD trial which was over 7,200 patients, a cardiovascular outcome trial, all under the umbrella of diabetic nephropathy. Now, what we did is it's the same design that you're looking at right there, and we did that so we could take all the patients, pool them as an individual patient level analysis; that is the FIDELITY analysis which is what I'm showing you here.

Everybody was on maximal-tolerated doses of a RAS blocker and then randomized to finerenone or placebo. It was over 13,000 patients and we had a cardiovascular outcome which was a major adverse cardiac events (MACE) outcome with heart failure hospitalization; we also had a renal outcome which was doubling of serum creatinine, an ESRD diagnosis, or renal death. You can see how much of the heat map is actually covered by this trial with a median follow-up of 3 years.

You can see here, on the left, the cardiovascular outcome with a 14% risk reduction. On the right, the kidney outcome with doubling of creatinine is a 23% risk reduction.

Those are the 3 pillars. What about a fourth pillar that's coming? Well, when you look at the combined consensus report, ADA/KDIGO, as far as GLP-1 receptor agonists goes, they have been established to reduce atherosclerotic cardiovascular disease or established kidney disease by reducing albuminuria. If you read the guidance here, it says an SGLT2 or GLP-1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimen, level 1A.

For patients with type 2 diabetes and CKD, who have not achieved individualized glycemic targets despite use of metformin and an SGLT2 or are unable to use these medications, a long-acting GLP-1 receptor agonist is recommended, level 1B.

These are strong statements about glycemic control with these agents, and I think we all know that they are amazing agents for glycemic control.

Module 3: Glucagon-Like Peptide-1 Receptor Agonists

John B. Buse, MD, PhD: Thank you, George. It's really a pleasure to get a chance to talk to you about GLP-1 receptor agonists. I've been working with this class of drugs since 1999 at the University of North Carolina. We were the first people to give a GLP-1 receptor agonist to patients with diabetes in a clinical trial. It's really remarkable where we've gotten to with regard to this class of drugs and its broad effects, not only on glycemia but weight and cardiovascular and renal endpoints.

Let's review the pharmacotherapy, and the first thing to remember about GLP-1 receptor agonists is they have very broad effects. We generally think about them first and foremost for their effects on the pancreas. They increase insulin secretion, but they also reduce glucagon secretion. Importantly, they do so in a glucose-dependent fashion. Subsequently, the intrinsic risk for hypoglycemia is essentially none. In all models, they seem to increase beta cell survival, but they also have effects in the central nervous system to increase satiety, reduce appetite and thereby produce weight loss. In the GI tract, initially these long-acting agents reduce gastric emptying. Over time, there's tachyphylaxis to that effect, but there is a general effect to reduce GI motility.

With the short-acting agents, they can reduce gastric emptying on a chronic basis because the tachyphylaxis doesn't develop. In the heart, there is a small increase in heart rate that's been uniformly seen across the various agents in the class, and a reduction in blood pressure as well as increased contractility. Most importantly, there's a reduction in cardiovascular endpoints. In the liver, there's reduced gluconeogenesis, in part related to the pancreatic effects and perhaps other effects as well.

One of the issues with the GLP-1 receptor agonists is, as a class, they're not exactly alike with regard to the actions that you should expect in an individual patient. Modern medicinal chemistry matches a small molecule to a receptor, and you're able to come up with multiple agents that have the same activity. This is peptide chemistry, and it's much harder to get the same action from every agent in the class. There are 3 ways in which these GLP-1 receptor agonists vary substantially: pharmacokinetics, structure, and size.

With regard to pharmacokinetics, we divide things into short-acting and long-acting agents. Exenatide twice a day and lixisenatide do not provide 24-hour coverage. Liraglutide is a once-daily molecule, but it has a sufficient half-life that it's working the next morning after you take an injection. The once-weekly products, exenatide once weekly, semaglutide, dulaglutide, (albiglutide is no longer available), all of those agents provide for a half-life long enough that, given once a week, at the end of that week there's plenty of drug still along.

Subsequently, it provides continuous coverage with the long-acting agents and discontinuous coverage with the short-acting agents.

The consequence of that discontinuous coverage of the short-acting agents is, first, they're not as effective for glucose-lowering or weight, particularly for fasting glucose. Second, they are associated with greater postprandial effects. When you take that injection, it's effective at keeping the blood sugar from rising after the meal. And third, because you have this intermittent exposure, you don't get the tachyphylaxis to the gastric emptying effect and therefore you tend to have more nausea, in general, with the short-acting agents.

With regard to structure, there's exendin-4-based therapies: exendin-4 was a salivary protein from a Gila monster. The Gila monster's exendin-4 (similar to GLP-1) is the backbone of exenatide and lixisenatide. Perfectly outstanding GLP-1 receptor agonist, but it just comes from a different place than the GLP-1 based agents which are based on the human GLP-1 structure. The consequence of that is that exendin-4 based agents are more likely to have antibodies, which can create some uncertainty when you don't see an effect. Also, there may be more issues with skin reactions than with the human-based agents.

With regard to size, we have smaller agents, and we have bigger agents. The large ones, albiglutide and dulaglutide, are fusion peptides: you take the GLP-1 structure and you fuse it with a big molecule, albumin with albiglutide and an immunoglobulin molecule with dulaglutide. These much bigger molecules don't penetrate the brain in the same way and, to some extent, that may drive differences, particularly with regard to weight and appetite signaling. The important point is that these agents are pharmacologically different, and we just need to take that into account when we're prescribing with individual patients.

The most important "not-exactly-alike" feature is that semaglutide is also available as a once-daily oral formulation. The same peptide that's used once-weekly with injectable semaglutide is administered once-daily as oral semaglutide with a carrier molecule that improves the absorption. There's still only about 1% absorption of the peptide, so we're using bigger daily doses. You get good exposure over a week with taking a tablet every day first thing in the morning on an empty stomach with 4 oz or less of fluid and then nothing by mouth for at least 30 minutes afterwards. It's a medicine that if you don't take it right, it doesn't work. Therefore, you must make sure that patients understand how to do that.

From the KDIGO and ADA collaborative guidelines, they have this wonderful table that goes through the various classes of antihyperglycemic medications and their effects; not only on progression of chronic kidney disease and effects on atherosclerotic cardiovascular disease and heart failure, but their glucose-lowering efficacy, their hypoglycemic risk, their weight effects and issues with regard to cost. Most of the focus in the KDIGO guidelines is on the SGLT2 inhibitors and GLP-1 receptor agonists and that's because these are the agents that have demonstrated benefits with regard to chronic kidney disease. However, for this section, we're focusing on the GLP-1 receptor agonists, and the benefit for progression of chronic kidney disease is generally in the area of reducing albuminuria or preventing the progression to albuminuria. There's less robust evidence about progression to end-stage renal disease. The atherosclerotic cardiovascular benefits are clear-cut and well demonstrated and, uniquely, this class has demonstrated a benefit on stroke.

With regard to heart failure, it's been characterized here as potential benefit. It seems that people without heart failure do seem to have a benefit with regard to developing heart failure, but in people with heart failure, the message is a little less clear. These agents, or the most potent of these agents, have the highest glucose-lowering efficacy of all the antihyperglycemic agents except, arguably, insulin. In fact, when you do head-to-head studies against insulin, they tend to tie and sometimes win, but the issue with insulin is you can deliver enough to cause hypoglycemia. Thus, if you're willing to have hypoglycemia, insulin arguably is more effective.

The hypoglycemic risk on its own is mostly nil. In combination with sulfonylureas or insulin, it does bring out the hypoglycemia effect of sulfonylureas and insulin. These agents, again, are arguably the most effective weight loss agents available for human use and the 1 downside to these agents is they do tend to be expensive.

The ADA/KDIGO guidelines also talk about key risk mitigation strategies, not only for metformin and SGLT2 inhibitors, but also for the GLP-1 receptor agonists; and we'll talk more about this in a moment. The key counseling is about educating patients to improve the tolerability of the drug, and that really is one of recognizing symptoms and modifying diet. It's intuitive for patients as long as it's called out in advance for patients and then, for prescribers, to prescribe as indicated in the package insert, starting with the lowest dose and following the titration schedule. Sometimes, we even titrate more slowly in people that are struggling more. There may also be a need to adjust background glucose-lowering agents, particularly the insulin and sulfonylureas. This may be true particularly in patients whose A1C, when you start the patient on a GLP-1 receptor agonist, is already less than 8% or less than 7.5%, because these are potent glucose-lowering agents.

The last part of the ADA/KDIGO guidelines that I want to go through is their recommendations around advice for dosing in patients with more advanced kidney disease. Exenatide and lixisenatide are cleared renally bringing forth strict limits to what we can do with exenatide and lixisenatide in the setting of advanced kidney disease. The recommendation is that you use caution when

initiating or increasing the dose of exenatide in patients with stage 3b kidney disease, an eGFR between 30 and 44 ml/min/1,73 m^2, and that we do not use exenatide in patients with stage 4 or stage 5 chronic kidney disease. With lixisenatide, the recommendation is that we do not use it in patients with stage 5 chronic kidney disease.

The other GLP-1 receptor agonists do not require dose adjustment as they are metabolized in the bloodstream to functional immunoassays and short peptides, and renal clearance has nothing to do with glycemic efficacy or side effects.

For a summary, there's a nice paper that was written a couple of years ago looking at the comparability of the various agents with regard to A1C lowering efficacy, weight and GI adverse events. We have a great benefit in this class that there have been head-to-head trials between almost all these agents to inform these kinds of rankings. With regard to glycemic efficacy, semaglutide is clearly the most effective GLP-1 receptor agonist with dulaglutide being a close second. With regard to effects on weight, again semaglutide, the most effective GLP-1 receptor agonist, particularly in the injected formulations, but also in the oral formulation. Liraglutide would be in a close second place, but as a once-a-day therapy. With regard to GI adverse effects, the highest rates of GI adverse effects are exenatide in the twice-daily formulation and the lowest with exenatide in the once-weekly formulation. The reason for that is that that once-weekly formulation has a half-life in weeks and, as a result of that, the levels build up very slowly after the initial administration, which results in a lower risk of GI adverse events. In fact, semaglutide does seem to have the highest risk of GI adverse events, but the truth is that all these drugs are associated with about 95% of people being able to tolerate the class of drugs with appropriate counseling.

How do we get to appropriate counseling? This is basically my script. I always talk to every patient where we're considering using GLP-1 receptor agonists about their advantages: great efficacy in lowering glucose, great efficacy in weight loss, effect on blood pressure reduction which are all things that patients with diabetes need. We discuss their compelling indications, which are people who have prevalent atherosclerotic cardiovascular disease or who are at high risk for cardiovascular disease. The reason why this is a compelling indication is that these drugs reduce heart attack, reduce stroke, and prevent mortality. That's been demonstrated for some of the agents, but not all, and we'll talk about that more in a moment.

With regard to adverse events, the big deal is the nausea, but patients can also have constipation, more rarely diarrhea. These generally resolve over time and are mild-to-moderate in intensity. I encourage patients to think about the GI adverse events in the context of satiety, meaning the sense of fullness that you get as you come to the end of a meal.

There are important safety issues that are covered in the package insert: gall bladder events, acute kidney injury, nausea and vomiting, in the setting of preexisting chronic kidney disease, and pancreatitis, which was not evident in the large-scale, long-term cardiovascular outcomes trials, but is in the label and would be a reason not to initiate therapy in a patient with prior pancreatitis. Also, the need in the setting of persistent nausea and vomiting to hold the drug and have the patient seek medical attention if it doesn't resolve over a few hours. This is a way of minimizing the risk of having a serious problem with gall bladder events, acute kidney injury, and pancreatitis.

The only contraindications are medullary thyroid cancer, multiple endocrine neoplasia or a family history of either one. It's not because these things are increased in humans, as far as we know it, but because in rats and mice, they do get medullary thyroid cancer at higher frequency. The whole story of how GLP-1 interacts with the thyroid C-cell is different in humans than rats and mice. We generally believe this is not going to be a big human problem, but that said, it's a serious black box warning in the package insert, and I would not prescribe this drug for patients with prior medullary thyroid cancer or multiple endocrine neoplasia or a family history thereof.

For dosing, always start with the lowest dose, go up slowly on the dose and back off for GI adverse events, perhaps taking another shot at increasing the dose later. I've listed, on this slide, different sorts of situations where 1 agent might be a better choice than others. I mentioned before that exenatide in the twice-daily formulation has the best postprandial efficacy. The once-weekly formulation of exenatide has the lowest GI adverse event rate. Liraglutide is the most titratable, arguably. Dulaglutide has the easiest injection to take, the nicest pen. Semaglutide, in the once-weekly formulation, probably has the highest efficacy, particularly for weight. Oral semaglutide has the advantage that it's oral, though it's not the easiest pill to take, based on the instructions that are required for its appropriate use.

Module 4: Case #1 – Robyn (Part A)

Robyn, a 58-year-old woman with a 10-year history of type 2 diabetes and an 8-year history of hypertension, is evaluated by her primary care provider for a routine follow-up. Robyn is currently prescribed metformin 500 mg twice daily, glipizide 10 mg twice daily, pioglitazone 30 mg once daily, and amlodipine 10 mg once daily.

Today's vitals reveal a blood pressure of 134/78 mmHg and heart rate of 86 beats/minute. Laboratory results reveal hemoglobin A1C increased to 7.7% from 7.2% and estimated glomerular filtration rate (eGFR) at 70 mL/min/1.73 m^2.

Robyn reports frustrations that her blood glucose levels are highly variable and that she is not losing weight (body mass index [BMI] = 34 kg/m^2) despite

exercising 30 minutes per day and reducing carbohydrates. Per patient report and blood glucose log, patient has experienced 3-4 episodes of symptomatic hypoglycemia in the last 3 months:

- Prebreakfast blood glucose readings average: 73 mg/dL (range: 58 mg/dL – 99 mg/dL)
- Postprandial blood glucose readings average: 192 mg/dL (range: 136 mg/dL – 248 mg/dL)

Which one of the following is the most appropriate next step in the management of this patient?

A. Decrease metformin to 500 mg once daily
B. Initiate insulin aspart 5 units SQ with each meal
C. Decrease glipizide to 5 mg twice daily with meals
D. Decrease pioglitazone to 15 mg once daily

The correct answer is C: *Decrease glipizide to 5 mg twice daily with meals*

Discussion:

- In managing patients with diabetes, it is important to reduce present discomfort (eg, hypoglycemia) to increase patient's motivation to prevent long-term microvascular and macrovascular complications.
- Episodes of frequent symptomatic hypoglycemia are a concern requiring reduction of the sulfonylurea.
- The addition of rapid-acting insulin would likely increase the risk of hypoglycemia. This patient is not appropriate for insulin therapy according to current guidelines. Insulin is initiated as basal first.
- Decreasing the doses of metformin and pioglitazone would not reduce the risk of hypoglycemia but would negatively impact glycemic control.

Module 5: Guidance & Guidelines for Type 2 Diabetes

John B. Buse, MD, PhD: this is a slightly broader conversation than what we've just had earlier today from George and my earlier comments. This is focusing more broadly on type 2 diabetes in general, and not so specifically on chronic kidney disease and the GLP-1 receptor agonists.

There's been an influx of international guidelines over the last 4 years, and you may ask, "Why do we need so many opinions about how best to treat diabetes?" We have had a lot of data become available, and I think diabetes care in the year 2022, 2023 is more different from 2018 than it was in 2018 vs 2010. We're moving fast in diabetes care. We can get things done we never could before.

The most recent guidelines are the American Diabetes Association and European Association for the Study of Diabetes Consensus Report. It was presented and came out online on September 23, 2022, published both in *Diabetes Care* and in *Diabetologia* and the citation is at the bottom of the slide. It's available for free online. It's about 30 pages long, and I think a remarkable summary, but I'm biased, I was one of the cochairs of the writing group!

In this figure, we promote the holistic, person-centered approach to type 2 diabetes. We have the patient at the middle. The goals of care are always the same: to prevent complications and improve quality of life. Arguably, that's the case for all chronic disease management. How we go about achieving that, in diabetes, is we now recommend 4 principal components of care. First, medications for glycemic management. Second, setting weight management targets and trying to approach that with lifestyle intervention, medications, and/or surgery. Third, cardiovascular risk factor management for everyone. Fourth, cardiorenal protection: choosing these glucose-lowering medications based on the presence or risk of cardiovascular and kidney disease. We're saying we should be doing all of this for every patient with diabetes.

These are the principles of care that are pointed out and in 1 section of the paper, we get into very practical approaches for how to deal with things like social determinants of health, psychosocial factors, and substance abuse. These are nuances that you need to keep in mind in the way that you approach individual patients. The holistic nature is not only dealing with these 4 components of care, but to make sure that you don't forget about these principles because, at the end of the day, it's the patient that has to take care of the diabetes and, at best, a provider, whether they're a primary care provider, a diabetes educator, a pharmacist or an endocrinologist, we need to coach our patients on how to change their life and their medication strategies to achieve the goals of care.

With regard to glycemic management, the nuance and subtlety that's different now is we choose approaches that provide the efficacy to achieve the goals. You can start patients on metformin as the first-line therapy or use 1 or more agents, including combination therapy, that will provide adequate efficacy to reach the goals and to maintain those goals. Also, we want to avoid hypoglycemia, particularly in high-risk individuals. Some of those high-risk individuals would be elders where hypoglycemia may raise concerns in the family about their ability to care for themselves at home alone, and people that are in potentially dangerous lines of work, like construction or driving.

In the area of weight management, every patient needs to have an individualized weight management goal. A variety of approaches are available, from lifestyle to medications and surgery. When you're choosing glucose-lowering therapies, consider regimens that have high to very high dual glucose and weight management efficacy if weight loss is part of the goals that you and the patient set together.

With regard to cardiovascular risk management, we don't break new ground here. We point out that the guidelines are well covered for cardiovascular risk

factor management in other areas. With regard to the cardiorenal protection, for chronic kidney disease, we suggest using an SGLT2 inhibitor with primary evidence for reducing chronic kidney disease progression. If that's not tolerated, contraindicated, or not preferred, you could use a GLP-1 receptor agonist as a second-best choice, and if that didn't work for achieving the glycemic targets, you can use the combination of the 2 as the best approach.

In patients with atherosclerotic cardiovascular disease or high risk, either GLP-1 receptor agonists or SGLT2 inhibitors with proven benefits and, again, if additional glucose lowering is needed, consider using both. In patients with heart failure, utilize an SGLT2 inhibitor with proven benefits.

As you heard from George with regard to the KDIGO guidelines, these 2 sets of guidelines that came out just a couple of weeks apart were highly aligned in every area. This is the full figure 4, so you might even think about posting this either on your desk or in the exam rooms because it would have a graphical way of reviewing all the areas of glucose-lowering, weight-lowering, and blood pressure-lowering. Showcasing that there's a strategy and recommendation in that regard from global authorities.

People have always appreciated the algorithm as a roadmap for how to use various glucose management strategies. In the beginning, focus on healthy lifestyle behaviors, diabetes self-management, education and support, and then focus on social determinants of health as part of the background. Here we have the cardiorenal goals on the left, and on the right the glycemic and weight loss goals. We're working through this roadmap from top to bottom, in everybody with diabetes all at the same time. If glucose requires more lowering to reach the glucose-lowering goals, you just stop, start back at the top and keep going down.

Module 6: Case #1 – Robyn (Part B)

Robyn, a 58-year-old woman with a 10-year history of type 2 diabetes, an 8-year history of hypertension and obesity (BMI=34 kg/m^2), is referred by her primary care provider to an endocrinologist for evaluation and management. One month ago, Robyn's primary care provider decreased glipizide from 10 mg twice daily to 5 mg twice daily, increased metformin 500 mg twice daily to 1000 mg twice daily, and continued pioglitazone 30 mg once daily and amlodipine 10 mg once daily. Despite these changes, Robyn continues to report episodes of hypoglycemia. The endocrinologist:

- Discontinued glipizide
- Initiated linagliptin 5 mg daily as patient is resistant to injectable therapy
- Initiated losartan 100 mg daily for blood pressure management in setting of diabetes
- Referred to dietitian for medical nutrition therapy

Over the next year, Robyn's hemoglobin A1C decreased to 7.1% and she had no further episodes of hypoglycemia. She is now being seen by her primary care provider for a routine follow-up.

Today's vitals reveal a blood pressure of 126/72 mmHg and heart rate of 84 beats/minute. Laboratory results reveal eGFR decreased from 70 to 52 mL/min/1.73 m^2 over the past 12 months and urine albumin-creatinine ratio (uACR) is increased at 80 mg/g.

At what stage is her kidney disease?

A. CKD stage I
B. CKD stage II
C. CKD stage IIIa
D. CKD stage IIIb
E. CKD stage IV
F. CKD stage V

The correct answer is C: *CKD stage IIIa*

Discussion:

- According to a study conducted in 2019 by Vistisen et al, the mean annual decline of eGFR after diagnosis of CKD stage III for patients with type 2 diabetes was 1.9 to 3.0 mL/min/1.73 m^2. A dramatic decrease of eGFR experienced by this patient (18 mL/min/1.73 m^2) may indicate rapidly progressive decline and warrants additional investigation and monitoring.
- According to KDIGO's CKD staging (heatmap): the patient's eGFR of 52 mL/min/1.73 m^2 and albuminuria of 80 mg/g indicate the patient has stage IIIa kidney disease with mild-to-moderately decreased eGFR (G3a) and moderately increased albuminuria (A2).
- It is pertinent for healthcare providers to discuss the KDIGO staging heatmap with patients to improve awareness, risk mitigation, and treatment adherence.

The primary care provider refers Robyn to a local nephrologist for further evaluation and treatment for her declining kidney function. Current medications:

- Metformin 1000 mg twice daily with meals
- Pioglitazone 30 mg once daily
- Linagliptin 5 mg once daily
- Amlodipine 10 mg once daily
- Losartan 100 mg once daily

Based on her stage IIIa CKD, which of the following changes should be made to the patient's medications at this time?

A. Discontinue metformin
B. Discontinue linagliptin
C. Initiate SGLT-2 inhibitor with cardiorenal benefit
D. Initiate GLP-1 receptor agonist with atherosclerotic cardiovascular benefit

The correct answer is C: *Initiate SGLT-2 inhibitor with cardiorenal benefit*

Discussion:

- SGLT-2 inhibitor with primary evidence of reducing CKD progression is recommended.
- A GLP-1 receptor agonist with atherosclerotic cardiovascular benefit is recommended for patients who do not tolerate or have a contraindication to an SGLT-2 inhibitor with primary evidence of reducing CKD progression. A GLP-1 receptor agonist can be added if the A1C is above target despite SGLT-2 inhibitor therapy.
- Although the patient's renal function has declined, the current metformin dose should be continued at an eGFR of 52 mL/min/1.73 m^2. At an eGFR of 30 to 44 mL/min/1.73 m^2, caution is recommended in initiating metformin and for patients currently on metformin, it is recommended to reduce to a maximum dose of 500 mg twice daily. Metformin is contraindicated for eGFR <30 mL/minute/1.73 m^2.
- Linagliptin does not require renal dose adjustments and should be continued.

Module 7: Cardiorenal Effects of GLP-1 RAs

John B. Buse, MD, PhD: It's important to talk about the terminology that we use here. MACE is Major Adverse Cardiac Events, and there's 2 commonly-discussed flavors, the 3-point MACE which is cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke. Then 4-point MACE is the same as 3-point MACE except it adds hospitalization for unstable angina or revascularization. A composite kidney outcome that's commonly used is the development of macroalbuminuria, the doubling of serum creatinine or at least a 40% decline in eGFR, kidney replacement therapy, like dialysis or transplantation, or death due to kidney disease. That's the broad composite kidney outcome that's often discussed. The narrower composite kidney outcome focuses on worsening kidney function, and that's defined by doubling of serum creatinine or at least a 40% decline in eGFR, the need for kidney replacement therapy or death due to kidney disease.

There are a bunch of cardiovascular outcome trials that were done in the setting of type 2 diabetes based on new regulatory guidance from the FDA. At the top is highlighted 4 of the trials that were done with DPP-4 inhibitors and you can see the yellow dots, which overlap, the number 1 is the hazard ratio and the bars is the 95% confidence interval. Therefore, dipeptidyl peptidase-4 (DPP-4) inhibitors had no effect on cardiovascular outcomes in the setting of type 2 diabetes patients at high risk for cardiovascular disease.

The SGLT2 inhibitor trials, with some heterogeneity, all show that the point estimate, the dot, is to the left of the 1, so there is some evidence for reducing cardiovascular events as evidenced by the 3-point MACE: nonfatal MI, nonfatal stroke and cardiovascular death. For all the SGLT2 inhibitors, the point estimate is to the left of 1. Sometimes the confidence interval doesn't cross 1, so we have a statistically significant effect with EMPA-REG for empaglifozin and CANVAS with canagliflozin, but not a statistically significant effect with the other 2. Though, in general, the trends are in the right direction.

When you look at the GLP-1 receptor agonists, there is more heterogeneity. Why is that? Remember how we talked in the very beginning: the GLP-1 receptors are not all alike and, in fact, some of the meta-analyses that I'm not going to show you actually exclude the ELIXA study with lixisenatide because it's a short-acting agent that was administered once a day in a different population. So there are potential reasons why some of these GLP-1 receptor agonists didn't seem to show benefit. In general, more of the dots to the left than what we see with the SGLT2 inhibitors and many of them have shown statistically significant differences with the hazard ratio not crossing 1.

When you look at the meta-analyses, here are each of the trials accompanied with the number of events, the number of patients with the GLP-1 receptor agonists and with placebo, and then the calculated hazard ratio further to the right. There is also the *P* value reported in the paper for statistical significance and, most importantly, at the bottom, the number needed to treat. What you can see is that with liraglutide, semaglutide in the subcutaneous formulation and dulaglutide, there was a statistically significant result. These are the agents that have cardiovascular risk reduction indications in their package insert. The dots are all to the left and some of them didn't reach statistical significance because they were really small studies; they weren't designed to show superiority and some of them didn't reach statistical significance because they didn't provide as much benefit.

When you look at other endpoints like cardiovascular death, fatal and nonfatal MI, fatal and nonfatal stroke, all-cause mortality, hospital admissions for heart failure, and composite kidney outcomes, what you see is that all of them are in the right direction, indicating a 10% to 21% reduction in these endpoints over moderate periods of time, averaging about 2.5 to 3 years. All of them show a trend. Most of them are statistically significant. The parameter of worsening of kidney function is not statistically significant specifically. There are very broad cardiovascular benefits and certainly benefits with regard to macroalbuminuria.

Finally, these meta-analyses also looked at adverse events in the cardiovascular outcome trials and when we look at severe hypoglycemia, retinopathy, pancreatitis and pancreatic cancer, we see that none of them had statistically significant results and that, in general, the point estimate for the hazard ratio or the odds ratio is very close to 1. Across tens of thousands of patients with fairly decent exposures, 2.5-3 years on average, we see a great profile of safety in this slide on top of the really important cardiovascular benefits on the previous slide.

So, George, let me let you take it from here with regard to the individual studies.

George Bakris, MD: Thank you very much, John. Let me talk to you about the effects of once-weekly semaglutide and once-daily liraglutide. Clearly, the administration is different here. One (semaglutide) is a weekly dose, the other one is a daily dose (liraglutide). These are from seminal trials that have been done, and these are looking at subsets of patients with albuminuria and looking at changes. When you look at the semaglutide/liraglutide pooled data over on the far left and you can see a reduction in albuminuria.

Likewise, when you look at the SUSTAIN 6 analysis here, you're getting nice reductions and LEADER, again you're seeing reductions over time, even though you're in the normal albuminuria range, you're still getting an effect that is seen.

When you're looking at this and looking at the data here in the context of what the GFR is, you're looking at all patients over on the far left, but let's look at the people in the middle with GFRs less than 60 ml/min/1,73 m^2. This is the group that you want to pay attention to. Also, there's a group with GFRs above 60 or at 60 ml/min/1,73 m^2 and you can see the effects. It's important to keep in mind when you look at semaglutide in the dark blue and liraglutide in the red, you're getting the greatest reductions in the people with advanced kidney disease. This is in patients with GFR less than 60 ml/min/1,73 m^2 where semaglutide seems to have greater reductions in albuminuria relative to liraglutide.

You're seeing an effect on albuminuria in patients with better kidney function, but if there's renal insufficiency, then clearly you're seeing the reduction, which is where you want to slow that progression.

This is a meta-analysis of GLP-1 RAs in cardiovascular trials. This looks at the composite of kidney outcomes, including macroalbuminuria. Macroalbuminuria is an old term, but it's not used anymore. These are people with GFR, with albuminuria of greater than 300 mg/day. Regardless of the trial that you're looking at, there is a benefit, especially with the longer-acting agents like SUSTAIN 6 and LEADER. Those agents clearly showed a benefit, REWIND, and even AMPLITUDE-O clearly show a benefit favoring the GLP-1 RAs.

What about looking at worsening kidney function over time? None of the trials that are on this list were designed with specifics in mind to look at renal outcomes. These were cardiovascular trials. At best, this is hypothesis-generating. If you look at the numerator on some of those studies, you can see it's small. You can see in general that nothing is going on the bad end and everything is trending towards either the line of identity or on the good side to slow worsening of kidney function**.**

Module 8: Multidisciplinary Management

John E. Anderson, MD: It's my privilege to talk about multidisciplinary management, about patient-centered care, and pillars of therapy. John made a great point about how rapidly information is evolving about the management of type 2 diabetes and now you have medications that were originally designed as antihyperglycemic agents which now have cardiovascular benefits, benefits in terms of reduction for hospitalization, for heart failure, and cardiorenal protection. Consequently, we don't get to sit in our silos anymore. There has to be communication between primary care, endocrinology, nephrology, and cardiology because we're all using many of the same therapies, and if you want to keep the patient at the center of care, then it requires that those of us involved in taking care of these patients be in communication with each other. When you do that, and when you do it well to the benefit of the patient, you have improved health outcomes for the patient and these patients have an enhanced satisfaction. I can't tell you how much more satisfied the patient is when they come in and they say, "Hey, you know, Dr. So-and-so from cardiology started me on this medication, and I say, 'Yes! I've already read the entire note, they gave me a call, and I see now that you've changed the medicine. How are you tolerating it?'" The patient is really satisfied that the members of the care team are communicating. It also goes to the fact that you're using resources more efficiently. People are not repeating the same lab tests. If I'm sending someone to a nephrologist, and I just ordered a urine albumin creatinine ratio (uACR) and an eGFR, I make sure the nephrologist has that information in their hand before they see the patient. While the nephrologist has the patient there, they can look at the labs. It mitigates the need for extra work being done. For those of us who are taking care of the patient, how much easier is it to walk in and see a patient when I know everything that's been done in the last 3 to 4 months? I'm completely on top of it when I walk in the exam room door. Not only is the patient very pleased, but it makes for a more efficient and enjoyable visit and because we can talk about everything that's going on with that patient and not just their cardiorenal disease and diabetes.

We need to use the multidisciplinary care team. Is it 1 organizational umbrella or a range of organizations? Is this someone at an academic center where everybody shares the same electronic medical record (EMR) or is it different EMRs and they're communicating via emails or faxed messages? Is this a primary care-centered basis where you have community health nurses and allied professionals? Whether it's the pharmacists, the certified diabetes educators (CDEs), the dieticians, or the specialists in medical care, it requires that we have an effective communication system, and it has to be agreed upon on how we're going to communicate with our care team about this individual patient.

Going back to that holistic, person-centered approach in diabetes management that John covered, the goals of care are the same in the patient as in the center and the ADA/KDIGO guidelines recommend overcoming these barriers. At the center of this is improved management of diabetes and the chronic kidney disease. We want to have harmonized clinical practice guidelines. All of us in primary care need to know what is expected of us. We need to refer to self-management programs. We need to do risk mitigation strategies, and we need to engage in education. The nephrologist may have a certain thing, and the nephrology nursing staff may want to educate the patient about something different than the cardiologist or the endocrinologist or the primary care provider. The education must happen from a multidisciplinary approach.

Module 9: Case #1 – Robyn (Part C, Conclusion)

Robyn, a 59-year-old woman with an 11-year history of type 2 diabetes (hemoglobin A1C 7.1%), is evaluated by a nephrologist in follow-up. The patient was diagnosed 7 months ago with stage IIIa chronic kidney disease with albuminuria. The patient was prescribed losartan and the SGLT-2 inhibitor empagliflozin for diabetic kidney disease standard of care, but she discontinued empagliflozin because of frequent genital mycotic infections.

Current medications:

- Metformin 1000 mg twice daily with meals
- Linagliptin 5 mg once daily
- Pioglitazone 30 mg once daily
- Amlodipine 10 mg once daily
- Losartan 100 mg once daily

Laboratory results reveal an eGFR 48 mL/min/1.73 m^2.

Which one of the following classes of medication should replace empagliflozin in this patient?

A. Alpha-glucosidase inhibitor
B. Glucagon-like peptide-1 receptor agonist with atherosclerotic cardiovascular benefit
C. Sulfonylurea
D. Basal insulin

The correct answer is B: *Glucagon-like peptide-1 receptor agonist with atherosclerotic cardiovascular benefit*

Discussion:

- Of these 4 classes of medications, only selected GLP-1 receptor agonists have demonstrated benefit in kidney outcomes. A GLP-1 receptor agonist with atherosclerotic cardiovascular benefit is recommended for patients who do not tolerate or have a contraindication to an SGLT-2 inhibitor.

After receiving education from the patient's nephrologist, Robyn is now amenable to injectable therapy if warranted. Current medications:

- Metformin 1000 mg twice daily with meals
- Linagliptin 5 mg once daily
- Pioglitazone 30 mg once daily
- Amlodipine 10 mg once daily
- Losartan 100 mg once daily

Which GLP-1 receptor agonist would be the best choice for this patient with chronic kidney disease?

A. Exenatide IR 5 mcg SQ twice daily within 60 minutes prior to meals
B. Lixisenatide 10 mcg SQ once daily x 14 days and titrate per directions
C. Semaglutide 0.25 mg SQ once weekly x 4 weeks and titrate per directions
D. Semaglutide 3 mg PO once daily x 30 days and titrate per directions

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The correct answer is C: *Semaglutide 0.25 mg SQ once weekly x 4 weeks and titrate per directions*

Discussion:

- Injectable semaglutide has been shown to confer kidney benefits, whereas oral semaglutide, exenatide, and lixisenatide have not.
- Liraglutide and dulaglutide, also shown to confer kidney benefits, are alternatives to injectable semaglutide.
- The decision to select a once-weekly or once-daily GLP-1 RA (with atherosclerotic cardiovascular benefit) should be discussed with the patient, and factors such as ease of administration, adverse effects, medication costs, and formulary options should be considered.

- In a patient that is highly resistant to injectable therapy, oral semaglutide can be a consideration, however, it is important to note that oral semaglutide has not been proven to confer cardiorenal benefits.
- Linagliptin should be discontinued as DPP-IV inhibitors and GLP-1 receptor agonists should not be used together due to similar mechanisms of action causing lack of therapeutic benefit.

Module 10: Case #2 – Jerry

Jerry is a 73-year-old man who presented to his primary care provider 2 weeks ago after being lost to follow-up for several years. He is now being seen in follow-up. Diagnostic evaluation reveals type 2 diabetes (A1C 8.7%).

Patient has a history of NSTEMI s/P PCI (8 months ago), hyperlipidemia x 11 years (LDL-C 53 mg/dL), hypertension x 14 years (BP 138/82 mmHg), and CKD stage IV (eGFR 19 mL/min/1.73 m^2). Patient is prescribed: empagliflozin, losartan, atorvastatin, aspirin, clopidogrel, carvedilol, and furosemide.

What additional information is pertinent to obtain from this patient?

A. Labs/Data, including uACR, potassium, BMI
B. Medication adherence history
C. Patient awareness of CKD significance
D. All of the above

The correct answer is D: *All of the above*

Discussion:

- The patient has history of CKD, therefore, related information such as uACR as well as potassium and body mass index may provide pertinent information to guide treatment options.
- According to a study conducted by Neuen et al, the combination of an increase in uACR and a decrease in eGFR was strongly associated with increased risk of advanced CKD than either parameter alone.
- An increase in uACR can be viewed as an inflammatory maker to portray the magnitude of kidney damage, whereas a decrease in eGFR is evidence of functional impairment.
- The patient has been lost to follow-up for several years, therefore, discussion on medication adherence is significant before decisions for medication therapy are made.
- It is of utmost importance that patients understand the natural history of their disease as this is often very motivating for treatment.
- It is also important to not reprimand the patient for being lost-to follow-up. Education is crucial to ensure the patient is empowered to work with the healthcare team to potentially alter the course of their disease.

Additional laboratory information reveals:

- uACR 160 mg/g
- K+ 4.8 mEq/L
- BMI 36.4 kg/m^2

Jerry W. indicates he is motivated to take better care of himself as he does not want to suffer another CV event. He is committed to following the treatment plan with his family's support. Current medications:

- Empagliflozin 10 mg PO once daily
- Losartan 50 mg PO once daily
- Atorvastatin 80 mg PO once daily
- Aspirin 81 mg PO once daily
- Clopidogrel 75 mg PO once daily
- Carvedilol 25 mg PO twice daily
- Furosemide 40 mg PO once daily

Which one of the following would be the most appropriate change to the patient's current medications?

A. Add liraglutide 0.6 mg SQ once daily
B. Add finerenone 20 mg PO once daily
C. Add metformin 500 mg PO twice daily
D. Replace losartan with hydrochlorothiazide 12.5 mg PO once daily

The correct answer is A: *Add liraglutide 0.6 mg SQ once daily*

Discussion:

- Liraglutide, similar to injectable semaglutide and dulaglutide, is a GLP-1 RA that has exhibited atherosclerotic cardiovascular benefit in patients with/or at risk for ASCVD and CKD. Per ADA/KDIGO guidelines, selected GLP-1 RAs can be considered as an option in patients with DKD who require additional glucose-lowering.
- Liraglutide is a viable option in patients that prefer once-daily administration and for those who experience nausea/vomiting since these adverse events resolve more quickly than once-weekly GLP-1 RAs.
- The decision to select a once-weekly or once-daily GLP-1 RA (with atherosclerotic cardiovascular benefit) should be discussed with the patient, and factors such as ease of administration, adverse effects, medication costs, and formulary options should be considered.
- The addition of a mineralocorticoid receptor antagonist (finerenone) to ACEI or ARB therapy provides additional benefit in kidney outcomes, however, finerenone is contraindicated in eGFR <25 mL/minute/1.73 m^2.
- Metformin is contraindicated in eGFR <30 mL/minute/1.73 m^2.

- ACEI or ARB therapy is standard-of-care for patients with diabetic kidney disease, therefore it is important to continue losartan in this patient.

What other healthcare clinicians should be involved in the care of this patient?

A. Cardiologist
B. Endocrinologist
C. Nephrologist
D. Pharmacist
E. All of the above

The correct answer is E: *All of the above*

Discussion:

- Multidisciplinary and interprofessional care is important to address the variety of health issues experienced by patients with type 2 diabetes, chronic kidney disease, and cardiovascular disease.
- Due to the patient's history of recent NSTEMI, hypertension, and hyperlipidemia, it would be beneficial to involve a cardiologist in this patient's care.
- Due to the patient's history of uncontrolled diabetes (A1C 8.7%), an endocrinologist can assist with adjusting patient's antihyperglycemic regimen. However, not every patient may be able to see an endocrinologist due to availability; it is important that primary care providers are educated to be able to work with the patient to directly address their treatment regimen for diabetes.
- Due to the patient's history of CKD Stage IV (eGFR 19 mL/minute/1.73 m^2 and uACR 160 mg/g), it is important to involve a nephrologist in this patient's care. It is recommended to refer a patient to a nephrologist when their eGFR is < 30 mL/minute/1.73 m^2. According to a study conducted by Kinchen et al, late referral (defined as less than 4 months from initiation of dialysis) was associated with greater burden of disease and reduced survival.
- This patient is on multiple medications and involving a pharmacist would assist with addressing potential polypharmacy, medication compliance, pharmacotherapy monitoring, and drug-drug interactions.

Module 11: Summary and Conclusions

John E. Anderson, MD: There's an urgent need for guideline-directed screening and early treatment of patients with type 2 diabetes and CKD. We talked a lot about how, in primary care, if you're going to properly screen for chronic kidney disease in diabetes, you must have both a uACR and an eGFR; that's something we must do every year. If it's abnormal, you need to increase the frequency with which we're monitoring.

The pillars of therapy to reduce cardiorenal risk include RAS blockade, SGLT2 inhibition, and a nonsteroidal mineralocorticoid receptor antagonist like finerenone. GLP-1 receptor agonists remain a potent option for glycemic lowering, cardiovascular risk reduction, and favorable data thus far on composite kidney outcomes, including macroalbuminuria. The ADA and EASD guidelines focus on a holistic patient-centered approach to managing type 2 diabetes and all the comorbidities. Effective person-centered care requires a multidisciplinary team. I can tell you from primary care that we can't do it all, nor do we have enough time with the patient to accomplish it all, nor do we have the expertise to address certain issues.

Make screening a priority in patients with type 2 diabetes. For years, we've managed blood pressure well. We've done well looking at low-density lipoprotein (LDL) cholesterols. We've done a good job of trying to drive hemoglobin A1Cs to target. CKD cannot take a backseat to those other 3 things that we're doing. We have therapies which allow a new opportunity to alter the course of CKD progression and cardiovascular risk. In primary care, we used to see somebody with a lower eGFR and some micro- or macroalbuminuria: we had nothing to offer them other than, "Please don't take anti-inflammatory medicines, be careful when you have any diuretics, and make sure you stay hydrated. We should be excited in primary care, especially because we have something to offer these patients and to change the trajectory of that disease state.

Always keep the patient at the center of the conversation. We don't need to talk down to patients. We need to be able to listen to patients and encourage and educate our patients. We need to continue communicating with our colleagues. The shared information system is of paramount importance in terms of making sure we're taking proper care of the patient.

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