[MUSIC PLAYING]

MARY KORYTKOWSKI: Thank you, Dr. Powers. Thank you, Dr. Resnick, for inviting me to participate in this year's conference. I am going to talk about new medications that have come into use for treating individuals with type 2 diabetes in the 21st century. But there are some 21st century updates on some of the older medications that I will go over as well.

Let's see now. Let's see me get my self organized here. OK, so I just have to disclose that I am on the Exam Committee for Endocrinology and Metabolism. And I need to tell you that I will not be disclosing any exam questions or answers, if any of you are coming up for recertification or new certification.

So what I want to do is go over the American Diabetes Association Standards of Care for Diabetes Management in Older Adults. You heard from Dr. Foreman earlier that the American Heart Association has not quite gotten around to putting out formal recommendations for the older adult population. But the American Diabetes Association has. This does not mean that we have a lot of data to support the recommendations. Much of it comes from consensus among committee members, but base it on the existing data that we have. And it is growing. And then I want to discuss the currently available oral and non-insulin injectable therapies that are available for treating people with type 2 diabetes, with attention to the risks that are summarized below.

So what are these therapies? So the 21st century medications are the sodium-glucose co-transporter 2 inhibitors. There's a lot of them. And they're the incretins, which include two classes-- the oral dipeptidyl peptidase IV inhibitors, which I'll now call the DPP-IV inhibitors-- and the glucagon-like peptide-1 receptor agonists. The 20th century medications that I'm not going to be talking about this morning include the sulfonylureas and meglitinides.

I will be talking about metformin. I will be talking about the thiazolidinediones. But I am not going to be speaking about those in the lower part of this slide because they play a very small role in treating type 2 diabetes. But there is new information about metformin and the TZDs.

The sulfonylureas-- I'm not opposed to using sulfonylureas in elderly populations. I think they can be safely used. But they have to be used carefully. And just like anyone who started on insulin therapy, patients who are started on sulfonylureas or short-acting insulin secretagogues also need to be aware of hypoglycemia-- what hypoglycemia feels like and how to treat it, and how to report it to their physician, so their drug regimen can be modified.

I'm going to start with this guidance statement from the American College of Physicians. I've been sitting in the audience this morning. And I know we are all bombarded with guidelines from so many different organizations. I mean, it's almost we choose the guideline that we feel makes the most sense to us. But the American College of Physicians just about two weeks ago published their own guideline for treating type 2 diabetes.

I do have to tell you that endocrinologists, the American Diabetes Association, the American Association of Clinical Endocrinologists, the Endocrine Society, have been in a bit of an uproar about this guideline. But it does have relevance to the population that we're talking about today. So I'm not going to address so much the controversy. But the guideline that was published two weeks ago has a lot of relevance for the older adult population.

The first component of this was that therapy should be individualized. I'm shortening what's being said here-- that the goal for therapy should be somewhere between 7% and 8%-- that therapy could be de-intensified if the A1C goes below 6.5%, but to be careful with this recommendation because you don't want to put people on a roller coaster of poor glycemic control than better glycemic control if they're doing well on current therapy-- and that in those with limited life expectancy, they're saying not to pay attention to the A1C. So I may take issue with that one. And what I'm going to propose for you or show you is the American Diabetes Association guidelines for older adults who are even in impaired health that are closely related to this, even though not exactly.

In creating this guideline, the American College of Physicians looked at four studies-- the UKPDS, which was published in the late 1990s-- ACCORD, ADVANCE, and the Veterans Affairs Diabetes Trial that were published in the early part of this century and which showed that in older adults with established type 2 diabetes who also had underlying cardiovascular disease, we should not be pushing therapy to get to A1C values of less than 6.5%-- that the risk for hypoglycemia increased, and that there was really-- unless you looked at subgroup analyses, and there have been lots of subgroup analyses from each of these trials-- that there was really no cardiovascular benefit. But each of these four trials tested a glycemic control hypothesis. They tested the theory that lowering A1C to near normal levels would reduce cardiovascular risk, which is going to be different from a lot of the trials that I'm going to be presenting to you this morning that are the cardiovascular outcomes trials, and looking at the question is, do specific agents benefit cardiovascular risk while also improving glycemic control?

So these are the trials. In your syllabus, there's a whole list of the trials. There's no way to go through all of them. It's kind of amazing the number of cardiovascular outcome trials there are in type 2 diabetes. But this slide kind of summarizes where we're going to go with these. So there have been several large trials with the DPP-IV inhibitors. They have all been negative in the sense that they have not shown cardiovascular risk reduction. They also haven't shown harm. So it's just been that there's been no reduction in cardiovascular risk.

In the GLP-1 receptor analogs, both liraglutide and semaglutide have been shown to reduce cardiovascular risk. I will show you this data. Exenatide and lixisenatide did not show any cardiovascular benefit, but also did not show any harm. And one could argue, if you so wish, that these are different populations. For example, the lixisenatide study was done in people within six months following a myocardial infarction.

The SGLT2 inhibitors-- empagliflozin and canagliflozin were two positive studies showing cardiovascular risk reduction and have become the darlings not only of the endocrinology world, but also of the cardiology world. Dapagliflozin that's a study that's still going on. And just within the past week, I received e-mails, just like probably all of you did, that yet another agent has been added to this class called ertugliflozin that I have absolutely no experience with whatsoever.

So this is the 2018 guideline from the American Diabetes Association for Glycemic Control. So here they are actually saying at diagnosis to initiate lifestyle management-- set an A1C target. So they're not saying the A1C target is less than 7%, although they will go on to say that for healthy younger adults with type 2 diabetes, that would be the target to minimize risk for microvascular as well as macrovascular complications, and that to initiate pharmacologic therapy based on A1C. Less than 9% use monotherapy. If it's greater than 9%, consider dual therapy. But the word here is to consider, not to automatically do that. And if it's greater than 10% or if the person is overtly symptomatic with hyperglycemia, to either start dual therapy or to do this in combination with insulin therapy, usually basal insulin.

Metformin remains the starting line for medication. And I'm going to talk about metformin a little bit later. But there is really no reason to abandon metformin as the first line agent. If the A1C is at the target that you've established for this patient and it is going to vary based on co-morbidities and age and a patient's functional status in older adults, there is going to be variation in the A1C you're aiming for. And then the recommendation is if they are at goal to monitor their A1C like every three to six months-- at goal usually about every six months-- and if they are not at goal, to assess are they taking their medications or to consider additional therapy.

And in the older guideline before 2018, there was the whole list. And you could choose from all of them. Now there's a little bit of a modification to that. All the modifications are there. And we'll come to those. But first, the glycemic goals-- for healthy older adults who are functional-- who have few co-morbidities-- the glycemic goal should be an A1C of less than 7.5%. For those who have complex or intermediate health, meaning they may need some help with activities of daily living or have two or more co-morbidities, a goal of less than 8% is considered acceptable.

And for those who have very poor or complex health, not only is the goal to avoid symptomatic hyperglycemia, but to aim for an A1C of less than 8.5%. This roughly correlates with a fasting glucose of 100 to 180. And a bedtime glucose of 110 to 200 is a way of avoiding overnight hypoglycemia, so pretty close to what you saw from the American College of Physicians, but still using goal-directed therapy, even for those with poor health.

There have been quite a few papers that have come out in the past two years that have shown we're probably overtreating people with type 2 diabetes. This was an examination from NHANES of adults greater than age 65 who were divided into a group who were healthy, who had complex or intermediate health, or complex or poor health, as defined by the American Diabetes Association. And you can see here that those in poor health had A1C values less than 7%. Now, not all of this was likely due to pharmacologic therapy. But they also looked at the prevalence of use of sulfonylureas and insulin according to each level of health status and found that there was as many people in this group with poor health who were on insulin or a sulfonylurea as there were in the healthy group, if not more, suggesting that maybe we need to look at what our therapies are. And maybe this is the group where we could be modifying our therapy to sort of reduce the use of drugs that are associated with hypoglycemia.

The American Diabetes Association now has a specific area in their Standards of Care for Management of Older Adults. And that table is included. One of their recommendations is that hypoglycemia be avoided in older adults with diabetes. It should be assessed and managed by adjusting glycemic targets and pharmacologic interventions. And this is Level B evidence, which isn't randomized controlled trials, but comes from extensive studies and secondary analyses of randomized controlled clinical trials.

So what's the next step? If you're not getting to the goal, whatever it is-- if it's less than 7.5% or less than 8.5% with metformin alone, unless metformin is contraindicated-- now the American Diabetes Association is saying look at whether or not they have underlying atherosclerotic cardiovascular disease. Well, as you heard from Dr. Foreman, just about everybody over the age of 65 has some form of atherosclerotic disease. It's going to be the rare person that doesn't. And if you throw in diabetes, even a larger percentage of people are going to have atherosclerotic cardiovascular disease.

So in some ways, it's a bit of a false choice. But they're saying to use an agent that has been proven to reduce major adverse cardiovascular events. And if you look at the agents that have been shown to do this, well, we have metformin from the initial publication of the UKPDS, as well as the UKPDS Legacy Study. We have the SGLT2 inhibitors, which have been demonstrated to reduce cardiovascular risk as well as congestive heart failure, and the GLP-1 receptor agonists, where liraglutide and now as well semaglutide has also been shown to reduce cardiovascular risk.

They say if there's no cardiovascular risk, then you should prescribe the next line of agents based on these specific patient factors-- risk for hypoglycemia, efficacy, the effect on body weight-- the cost, which is a major effect, particularly in the elderly who are on Medicare and can find themselves in the donut hole very early with the cost of some of these medications-- potential adverse effects. And another very important factor that I left off this slide is really patient choice here-- that it's important to discuss with them where you're going with their medications.

So let's just talk about the SGLT2 inhibitors. So the SGLT transporters actually are responsible for reabsorping glucose from the nephron. The SGLT2 inhibitors block these transporters from reabsorbing glucose. So normally, glucose will be reabsorbed up to a level of 180 to 200 milligrams per deciliter. When plasma glucose levels exceed this, there's glucosuria. These agents block the absorption of glucose at even lower levels of hyperglycemia, which allow people to lose glucose in the urine and actually create the symptoms of polyuria and polydipsia, which is something that we're supposedly trying to avoid in our patients as well.

There are now four agents in this class. They reduce A1Cs by about 1%. When used alone, they do not cause hypoglycemia. They are associated with weight reduction of 2 to 4 pounds, usually of 1 to 2 kilograms. Their side effects need to be taken into consideration, where they do increase the risk of genitourinary infections, including UTI and pelvic infections. They are associated with dehydration because as people lose glucose through the urine, they're also losing free water. So the elderly population in particular has to be informed that they need to keep up with fluid losses.

Canagliflozin has been associated with an increase in risk for lower extremity amputations and fracture risk. The data is in your syllabus. I don't have time to go through all the data. But the other agents have not been shown to create this. But the cost is very high.

But the reason why we need to talk about them is because this is the class of agents that has really opened the door to using diabetes agents that have been shown to not only treat diabetes-- they also have favorable effects on blood pressure. And they also have favorable effects on cardiovascular risk reduction. So this is the landmark trial. This is the one that started the whole conversation. It was published in 2015 with empagliflozin.

You can see there were over 7,000 subjects. They were randomized to placebo or one of two doses of empagliflozin. There were really no significant differences between these two doses, so we've been using the 10 milligram dose for just about everyone. The study lasted three years-- so a little shorter than the UKPDS was. But subjects were older. This is an older patient population. This is going to be true for all these cardiovascular outcome studies that I'll be showing you.

And they were mostly with Class 1 obesity. So the A1C levels were reduced by about 0.8% to 1% with both doses of empagliflozin. Systolic blood pressure decreased 4 millimeters of mercury and diastolic blood pressure about 1.5. There was a 2 kilogram reduction in waist circumference also decreased.

These are the outcomes data. So this is the composite outcome of cardiovascular death, nonfatal MI, and nonfatal stroke. There was about a 30% reduction over time with both groups of empagliflozin. These are the two groups put together. When they looked at individual outcomes, this is death from cardiovascular causes where there was almost a 40% reduction. Death from any cause-- again, about a 35% reduction, and hospitalization for congestive heart failure, which you heard about earlier from Dr. Matir, there was about a 30% reduction.

Now, there is one thing I want to call your attention to on this slide. And that is the fact is we usually think that if we're treating patients to reduce risk for microvascular and macrovascular complications that it takes time to achieve a benefit when you're using certain drugs or aiming for certain levels of A1C. But you can see here in this particular trial and in some of the other trials I'll be showing you, there's already a benefit being seen here within six months. For cardiovascular death, there's a benefit being shown even at three months. So it's quite impressive that we can impact cardiovascular morbidity and mortality at such an early level. Hospitalizations for heart failure-- almost immediately when they start this, and it's probably due to the combined diuretic effect and the blood pressure lowering effect as well. There's also some thought that there may be some remodeling of myocardial tissue.

So this study alone led the FDA to approve empagliflozin with the trade name Jardiance, for not only treating type 2 diabetes, but for minimizing cardiovascular risk in patients with type 2 diabetes. So it has this FDA approval. So I think that's why we're seeing so many drugs come out in this class. Everyone wants this approval because there's so many people with diabetes.

This is the results from the Canvas Study, which is really a combination of two different cohorts. But they presented these results at last year's American Diabetes Association. They also saw a significant reduction of about 15% in the primary outcome of risk reduction for death, nonfatal MI, and stroke. And this was over 10,000 patients. They also saw this early reduction in risk for heart failure. The reduction in deaths from any cause came later.

But they also saw, as did the empagliflozin study, showed a reduction in risk for progression of albuminuria and a decrease in renal outcomes. This was a composite of renal outcomes that included decline in GFR, the need for renal replacement therapy, or death from renal causes. So this is another thing that has made these studies of interest. You can see here it took a little longer to see the benefit with the renal outcomes than it did for the benefit from congestive heart failure.

But there are disadvantages that need to be kept in mind when prescribing these drugs. There have been case reports for euglycemic diabetic ketoacidosis. When you look at these cases, many of them look like they were more like a type 1 type of patient. They were often patients who were on insulin therapy. But because they lower glucose levels, they also reduce insulin secretion by the pancreas. And glucagon levels rise.

And they actually can have a direct effect on alpha cells within the pancreas to elevate glucagon levels, which are some of the causes that have been proposed for this increase in euglycemic DKA. This went through an extensive review by the FDA to see if there needed to be a black box warning put on. They thought that the cases are actually rare. But it's certainly something to keep in mind if you have a patient who is not feeling well.

There's high risk, particularly in the elderly population, for volume depletion, hypotension, and dehydration. So use this carefully in patients who are elderly and those who are using diuretics. Canagliflozin, as I mentioned, was associated with a higher risk for fractures. And lower extremity amputation's significantly higher when compared to the placebo group. And these agents are meant to be used in people who have essentially normal renal function.

Their efficacy declines as EGFR declines. And once EGFR declines below 45, there's really no efficacy with these agents for glycemic lowering. And whether it's cardiovascular risk reduction, we really don't know because the studies haven't been done in those people. Another thing-- because they cause polyuria, they should be used cautiously in men who have BPH. And a big issue is cost.

The glucagon-like peptide receptor agonist-- now we have five. I think I have just four in your slide. But exenatide in the cardiovascular outcome trial here was negative. With liraglutide and semaglutide, it was positive. Exenatide and dulaglutide can be given once a week as can albiglutide.

Sorry-- liraglutide is daily. Semaglutide is a weekly agent. Their efficacy is high. They have about 1% reductions in HbA1C. The risk for hypoglycemia is low, unless used in combination with sulfonylureas or insulin. They are associated with significant weight loss. And in fact, liraglutide is approved as a weight loss agent for people with and without diabetes.

Side effects-- there's a high incidence of nausea and vomiting that goes away. I'll show you some data about that. There are post-marketing reports of pancreatitis and acute renal failure-- but again, case reports. But again, the cost is high with these agents.

This is the results from the leader trial-- again, a very large trial-- a patient population with high risk for cardiovascular disease. But there were significant reductions in the primary outcome-- again, same composite-- cardiovascular death, non-fatal MI, and non-fatal stroke. But there was about a 13% reduction in the liraglutide group compared to the placebo group. It took a little longer to see the benefit. This is after a year of therapy.

There was also a significant, although less robust, reduction in death from cardiovascular causes. And this was a less robust, but again, significant, reduction in death from any cause. But this took several years to see that result.

Semaglutide-- these results were just recently published in the *New England Journal.* Again, they saw robust reductions in the primary outcome. But when it came to looking at am I alone, this was not significant. But non-fatal stroke was significant. There was no reduction in death from cardiovascular causes. So within the composite outcome, there were areas that were seen.

It's nice because it's once a week. Weight loss was significant But there's a couple of things to keep in mind with semaglutide because I have not personally started using this agent yet. And I have some reservations about it.

Again, similar to the results-- actually, with liraglutide and the SGLT2 inhibitors, the rates of worsening nephropathy were lower. But here with semaglutide, this was the one agent that was associated with a higher rate of retinopathy complications, including-- and not minor microaneurysms or dot and blot hemorrhages. There was a significantly increased risk for vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent. The hazard ratio was 1.6. And it reached a P 0.02 level. Similar to other GLP-1 agents, more patients discontinued semaglutide due to GI side effects.

What about older adults? So most of the patients in these trials have been older. They've all been over the age of 60, with a large percentage being above age 70. But this was a study that was done specifically in an older adult population with the agent lixisenatide. It was not a cardiovascular outcome trial, but basically an efficacy and safety study in an older population.

350 participants-- a mean age was 74. 37% of patients were above age 75. 11% were above 80. 28% had an EGFR of 30 to 60. So they had at least Class 3 CKD. And a fairly large percentage were on insulin, sulfonylureas, or other diabetes medications.

So once again, there was this 0.8% reduction in A1C. These are the placebo groups before and after. This is the lixisenatide group before and after. This is the 7-point glucose profile. So definitely efficacious in this patient population.

What about side effects? Well, again, nausea was very common in those receiving lixisenatide. But the incidence of nausea decreased over time. And this is using an intent to treat analysis. And it would include those who dropped out because of nausea. But the dropout rate was, in fact, very low. And typically, what we see is that the nausea is mild, short-lived, and does improve with continued use.

So again, about 6% dropped out in lixisenatide versus 1% in the placebo group. The other thing that was different here was there was a difference in hypoglycemia. But what I can tell you is that they did not adjust doses of insulin or sulfonylureas with the initiation of lixisenatide in this blinded trial. So I think this study just informs us that if and when we start patients on one of these agents to consider reducing any dose of insulin or an insulin secretagogue is a way of avoiding hypoglycemia.

The dipeptidyl peptidase-4 inhibitors-- once again, no cardiovascular risk reduction. But they are also used frequently because they're easy to take. The side effect profile is low. They have been known to infrequently cause URIs or UTIs. That's been shown with sitagliptin. Some people feel headache or muscle aches. It's not frequent, but it does happen.

There are rare LFT elevations. But that's more with vildagliptin. That's not even on the market here. There are case reports of acute pancreatitis. So there's definitely a signal there, even though it doesn't really reach significance in a lot of the trials.

And there are rare case reports of hypersensitivity reactions that are actually life-threatening. But they're very rare. The cause isn't really known. Again, cost is high. They can be taken with or without food. They're taken once a day. Saxagliptin was shown to be associated with an increase in risk for congestive heart failure admissions.

This is a subgroup analysis of people above the age of 65, or they were above the age of 75, from one of the large cardiovascular outcome studies to just look at safety and efficacy in the older adult population. So this is a study done with sitagliptin-- and basically comparing patients greater than age 75 in the solid line compared to those less than age 75, there was a sustained reduction in HbA1C that continued for the duration of the study.

I know this kind of a slide is hard for you to read-- but it's looking at basically cardiovascular outcomes, as well as adverse effects. The only thing here that really your attention is called to is the risk of pancreatitis, which crosses 1, meaning it was not significant. But certainly there was a signal there for it. But everything else really was not significant. So no cardiovascular benefit-- no major side effects here in this trial.

I just want to talk about metformin in 2018. So it's been around a long time. You know the drug. I know the drug. It's been around in the world since the 1950s-- in the United States, since the 1990s.

The risks of lactic acidosis are extremely rare. Actually, I did not include this trial. But even last week in the March issue of *Diabetes Care,* there was a study comparing the use of metformin in people with advanced CKD. And they based the dose differently depending on the level of CKD, but all the way Class 3 and Class 4, and found that metformin levels were [INAUDIBLE] Lactate levels were similar in these groups.

So we're learning more about the safety. This lactic acidosis has always been sort of over our heads as a scary thing about it. But it is extremely rare in people with type 2 diabetes. You now know that you can use it safely to EGFRs of 45. But usually dose reductions are recommended as EGFRs decline below 45, and then to stop it if it goes below 30. It's not recommended to start metformin if the EGFR is less than 45. But you can continue it if someone is already on it. But if somebody's on 2,000 milligrams a day, I usually decrease them to 1,000 milligrams per day.

Now, what's new about metformin? This is something from the *New York Times*-- that it is being looked at as the longevity drug. It's being looked at in a lot of other disease states now besides diabetes. I thought this was an interesting sentence that I took out of the article about metformin, but that many scientists and doctors are actually dosing themselves with metformin, as they think it's going to prevent aging and protect their cells from wear and tear.

And there are animal studies that have been shown that metformin extends the life span and health of mice. Whether it does this in humans or not, I'm not really sure. I can say that nothing has jumped out at me in my clinical practice about this since treating people who are older since the 1990s with this drug. But it's interesting. So there actually are several studies, one of which is the Targeting Aging with Metformin Study-- is recruiting greater than 3,000 people with age 65 with or without risk for cancer, heart disease, or cognitive decline, which there aren't many people who aren't at risk for at least one of these.

Why? Why are they looking at metformin? Well, in addition to all its glucose-lowering properties, it's been demonstrated to have antioxidant and anti-inflammatory effects. It activates sort of the energy generator within the cell of AMP kinase-- A-M-P kinase. It inhibits mitochondrial complex 1, which that will be kind of a extensive discussion. And it reduces the production of reactive oxygen species. So sometimes I wonder if I'd ever have something new to present at this conference. But I think, stay tuned.

Oh, I still have a minute. So thiazolidinediones also have been around for a long time-- just new information about pioglitazone. And I think none of us are using rosiglitazone anymore after all the controversy about whether it did or did not enhance cardiovascular risk. But pioglitazone was studied.

This was a non-diabetic population who had evidence of insulin resistance following a stroke. It's the IRIS trial. Subjects were randomized to pioglitazone or a placebo. And what they found is that event-free survival was significantly greater in those receiving pioglitazone compared to those receiving placebo.

The other area where pioglitazone has been shown to be useful that's relevant to people with type 2 diabetes is it's the only diabetes agent that has been shown to reduce some of the changes seen with non-alcoholic fatty liver disease. When looking at secondary outcomes, there was a reduction in the risk of progression to type 2 diabetes. But certainly, the cardiovascular events were not different.

But there was adverse events similar to what has been seen in other trials using thiazolidinediones, including an increased risk of fractures. For some reason, heart failure was not so much an issue. But these patients were carefully monitored. But they did not see any increased incidence of cancer, sort of relating to the fact that an increase in bladder cancer has been observed in some studies with pioglitazone, although this does not seem to be bearing out.

So just to summarize, it is recommended that diabetes management in older adults and probably younger adults as well be individualized according to glycemic goals, according to their functional status, and other co-morbidities. The 21st century medications offer some cardiovascular benefits, but not cost advantages over the 20th century medications. There's new data relating to the 20th century medications that support recommendations for metformin to be used as a first line agent in the absence of contraindications and reconsideration of how we use pioglitazone.

And the question to be answered in the future is is metformin an anti-aging drug? Stay tuned. We'll find out. But even if it isn't, it has been shown to reduce cardiovascular events. It has a low risk for hypoglycemia. It's affordable. And it makes it a good choice as a first line agent. So thank you for your attention.