MARY KORYTKOWSKI: So good morning. And thank you to the organizers for the committee for inviting me to come back. There is a lot that's going on in the world of diabetes, a lot with medication use. I plan to talk about some of the new medications and some of the new studies. I'll also be talking about a study that is hot off the press. It just showed up in my inbox yesterday.

I actually had the study several weeks ago. I was on the adjudication committee for the study so I did get it ahead of time. So I didn't make slides at 1 AM for this particular study. So I am going to try to focus on what some of the highlights are, rather than go through everything in a lot of detail.

You heard that your attention span is about 35 minutes. We have to match that to speakers who have trouble limiting their talks to 35 minutes. But I have made an effort to try to do so, so hopefully will not go over and interfere. I'll try to time myself here.

OK. So you already heard my disclosure. I'm not going to even go through the objectives of what we're going to do, but I probably-- this is no news to anyone in the room, that diabetes is very common in the elderly population. It affects one out of every four to five people, depending on the study that you look at, in people above the age of 65.

If you look in impaired glucose tolerance or pre-diabetes the rates are even higher. But I'm not going to even go into that discussion. I'm going to focus on diabetes.

The things that can further complicate management of diabetes is that there's also a high incidence of CKD that I'm sure you're going to be hearing about in the next couple of days. There is a high prevalence of dementia. The older the population goes, the higher the percentage of the population that has dementia.

Decreasing vision, poor dentition, decreased appetite, polypharmacy, frailty, the inability to get around very easily. And probably most importantly is this issue of limited financial resources. There are some people who are well-insured. There are really wonderful new medications out there for treating people with diabetes. And I am going to talk about them as I would talk about any medication-- about how they work, what their advantages are, and what their disadvantages are.

But cost is a real issue when it comes to these new medications. And even though I may speak negatively about some of the older drugs, I hope you'll understand that I use some of the older drugs that I may speak negatively about when cost becomes an issue. Because that in and of itself is a major stressor for our patients.

So this is a summary of some of the data from the consensus conference and all the older adults that was held by the American Diabetes Association, that I had the opportunity to be a member of the writing group. And we argued a lot and discussed a lot. And then this was one of the tables. I think it's actually-- there was lots of controversy about it as we were coming up with it.

When I go back to this table-- it actually exists for lipids and blood pressure as well. I love this table. I actually think it helps put into text what we deal with every day, when we're dealing with these patients who have multiple issues or the geriatric syndrome. So for people who are healthy-- and there are the healthy older populations who are going to live to beyond 100, and they'll be exercising every day-- the goal A1C is to be less than 7.5.

Some of the discussion came-- well, if somebody has an A1C of 6.9 does that mean we have to get them higher? And we thought, no. If you're doing well with a lower A1C there's no need to relax your glycemics control strategy. But that 7.5 should be about the range that you would wait to before you intensify therapy further.

This correlates with the fasting blood glucose that ranges between 90 and 130, and a bedtime blood sugar of 90 to 150 to avoid overnight hypoglycemia. Probably the majority of people above the age of 65 fall into this category, where they have some other co-morbidities that they're dealing with such as osteoarthritis, hypertension, hyperlipidemia, or heart disease.

And they have an intermediate life expectancy. No one really knows for how long. But here it would be reasonable to wait until their A1C is closer to 8% before you start intensifying therapy. Again, corresponding to a fasting glucose of 90 to 150, and a bedtime blood sugar of 100 to 180.

For those who are in very poor health, or in a nursing home with very limited life expectancy, or for whom too much medication may become too much of a burden, 8.5% is probably acceptable. Now there's a lot of discussion around this point. And the American Geriatric Society is even suggesting that we allow A1Cs to go back up to 9% in this population.

My difficulty with that kind of a goal is not a strong one. But when we set a goal of 8.5% we usually wait till it gets there before we make changes, or it gets a little bit above. With 9% we may be letting it get a little bit above 9% before we intervene. But the American Geriatric Society and the American Diabetes Association are very close to each other with their recommendations.

And then this is the recommendations for the American Geriatric Society, which it's very much the same, but as I mentioned here it was allowing a goal of up to 9% for patients with multiple co-morbidities. And they actually add in the statement that by trying to drive the A1C down to below 6.5% or 7%, as has been recommended for young adults with type 1 or type 2 diabetes. We are really increasing the risk for hypoglycemia in all its associated morbidities.

So I based this talk on a. paper that I'm actually working on with Dr. Dan Foreman, who I expect will be speaking at this conference in the next day or two, where we're working on a paper talking about modifying cardiovascular risk in older adults with diabetes. And I'm going to very much focus on the diabetes management part. But when we look at the glycemic management, blood pressure management, and lipid management we look at diet, exercise.

I think sleep is an overlooked lifestyle intervention. Inadequate amounts of sleep contribute to all kinds of risks as well as can elevate the blood sugars. I'm going to talk about not only glycemic goals, but also choice of agents.

I think what has been unappreciated is the role that hypoglycemia plays not only in contributing to issues like falls or strokes, but that hypoglycemia itself is a cardiovascular risk factor. In the past couple of years there's been really the very interesting data coming out showing that this itself actually can cause cardiac problems or strokes.

I'm not going to say much about lipid lowering therapy, blood pressure, or aspirin in this particular talk, but these are also important considerations in older adults, as well as younger adults. So when we're talking about glycemic control we're talking about the issue of balance. And the older adult population is really a key group where this issue of balance-- of doing good without doing bad in this population. So balance is certainly an issue in so many things.

This little cartoon of what kind of control to aim for has been used for several years. It was published by one of the authors of the Acorde study, but I think it tells the story. And I would think that most of our older adult population would fall somewhere here in the middle to your right, where they will have risks associated with hypoglycemia or other adverse drug events which is going to be towards the higher end.

People who are older adults can have newly diagnosed diabetes as well as longstanding diabetes, so they could actually come anywhere along the spectrum. Those with newly diagnosed younger patients we usually aim for tighter control. Those with longstanding diabetes who usually have multiple co-morbidities, less stringent control.

Life expectancy is going to be sort of the older we get, the shorter our life expectancy. Although the longer we live the longer we're likely to live. Having co-morbidities. We've talked about having established vascular complications. Older adults with diabetes are enriched with cardiovascular disease.

Patient preference for treatment is actually an often overlooked issue, particularly when we try to meet these quality standards. But some patients just don't want to be under tight control, because they're fearful of complications or they don't want to be on too many medications. And then what resources are available to support patients as you try to pursue control of blood pressure lipids and glucose levels.

Now another series of publications that has been coming out-- this is one of them. There are others from different populations. These are patients from the VA health system. So I'm actually telling you that, really, for healthy, older adults, having an A1C up to 7.5% is absolutely fine.

These are close to 700,000 patients treated with insulin or sulfonylurea above the age of 75, with a creatinine above 2, or cognitive impairment, or dementia. And as you can see, about 50% of patients in this particular patient population on insulin and sulfonylureas. So these are the two agents that put people at highest risk for hypoglycemia-- have A1Cs below 7%.

And you can see about 10% to 15%, depending on the network that they're in. But it's pretty equal among the different sites-- have A1Cs below 6%. These would be groups where it would be well-advised to relax their glycemic control a bit.

The hospital admissions in older adults for hypoglycemia far exceed hospital admissions for hyperglycemia. I think this is actually data from NHANES, where here is the number of hospital admissions per 100,000 patient years in age groups 65 to 74.

And then you get into age 75 and above. There is over 150 per 100,000 population, where the risk for hospitalization for hyperglycemia is 100. And it actually has gone down over time, probably as we've pushed our glycemic management.

As I mentioned earlier, there are studies showing that hypoglycemia is a risk factor for cardiovascular disease. This is not our work. But this is in a review paper that we wrote that summarized the work of others, where these very interesting studies have been done where people have been put on continuous glucose sensors and Holter monitors at the same time. And worn them for several days. And no interventions were done. It was just a monitoring study, although it was an older adult study, middle-aged to older adults.

When hypoglycemia occurred-- this would be a blood sugar of less than 70 milligrams per deciliter overnight-- at nighttime there was an increase in heart rate. There was actually more associated bradycardia so just the opposite. It seemed that the tachycardia was followed by bradycardia, increased atrial ectopy, increased ventricular ectropy, and prolongation of the QT interval.

This might be some of what could explain some of those early morning MIs that we see in some patients, particularly those with diabetes. In the daytime-- hypoglycemia in the daytime-- there were more ventricular premature beats and prolongation of the QT interval.

The duration of hypoglycemic events in the daytime was much shorter than the duration of the hypoglycemia events that occurred overnight, often because people are awake, and working, and more aware of their surroundings. And actually sleep alone, even in healthy people with diabetes, is a risk factor for hypoglycemia.

When they looked at hyperglycemia with blood sugars above 250 milligrams per deciliter, there was very little in the way of cardiac problems. There was a little bit of an increase in ventricular premature beats during the daytime. And overnight there was really no arrhythmias associated with hyperglycemia.

So I think this kind of a study is a wake-up call to what can be happening to our patients. We always have thought of hypoglycemia as being an acute event, that you take care of it, and it's over. But in fact, hypoglycemia in and of itself can be associated with just what we're trying to prevent, which is vascular disease in these patients.

So this is the grid that we work with for deciding what agents to use for treating with people with diabetes. We start with metformin. I'm going to tell you a little bit about metformin here today. And then at metformin the door is open to several different agents for second line therapy. And then depending on what you use for second line therapy, what you do for third line therapy and beyond.

I'm not going to dwell on this slide, but the factors to take into account are efficacy of the agent you're adding, the risk for hypoglycemia. Is there any associated risk for changes in weight? And weight gain is what we worry about more than weight loss. What is the risk of side effects and what are the costs? And we'll come back to this slide towards the end.

So sulfonylureas. They've been around for a long time. We use them all the time. Sulfonylureas are the long-acting agents. Glipizide and glimepiride are the two that are used the most frequently. I really hope that glyburide is disappearing from the map.

The most common side effect for all these agents is hypoglycemia. The risk for hypoglycemia increases as the serum creatinine increases. Glyburide is a particularly noxious agent for use in the elderly, particularly in the presence of CKD. Because its half life can be as long as 36 hours, meaning that any hypoglycemia event can go on for quite a long time.

The meglitinides are short-acting insulin secretagogues. Grogs. The two that are available are repaglinide and nateglinide. I really never used nateglinide. Repaglinide I do use periodically in people who have irregular meals. And you can start at very low doses of 0.5 milligrams before a meal. The half life is shorter.

It's efficacy is more on post-prandial glucose control. But in meta analyzes, it's been shown to have similar risks for hypoglycemia as the sulfonylureas do. But when used cautiously and individually, I think we can minimize the risk for hypoglycemia.

This is a study that was just published last year in *GM Internal Medicine.* It was looking at people who had come to the hospital for hypoglycemia. There were over 97,000 emergency room visits for hypoglycemia. People above the age of 65 accounted for about 40% of all emergency room visits for hypoglycemia in the United States.

The drugs most commonly used in these populations were sulfonylureas and insulin. And people above the age of 80 were more likely to be hospitalized than any of the younger age groups, and would have prolonged hospitalizations.

This is a study of patients in long-term care facilities, where 150 subjects who had A1Cs above 7.5-- which was probably too low of a target to start that at, or had two blood sugars above 180-- were randomized to receive basal insulin plus correction insulin. Or oral agents plus a sliding scale insulin. The basal plus group was getting sliding scale insulin as well.

Glycemic control was achieved in both groups, but when you look at these standard error bars they sort of are dropping to levels where it doesn't really feel very comfortable. So glycemic control was achieved, but at the expense of a 30% incidence of hypoglycemia in both groups.

So this is really just demonstrating that insulin and sulfonylureas are associated with high risk for hypoglycemia in elderly population. I really don't want you to leave here today saying never to use these. But when they're used, to use them very cautiously, and not to drive people down to low levels of A1C. The incidence of severe hypoglycemia was low, but even mild degrees of hypoglycemia can be associated with cognitive impairments.

Metformin. I wanted to just spend a few minutes talking about metformin, because we hear still-- this is still the black box warning for metformin-- is that it is contraindicated in renal disease or renal dysfunction. And not to use it with serum creatinine that's above 1.5 in a man or 1.4 in a woman. And that it should not be initiated in people over the age of 80, unless measurement of creatinine clearance demonstrates that renal function is not reduced.

This labeling has not changed. So what I'm about to say, please keep this in context, because I don't necessarily follow this. I do follow what I'm going to be showing you.

There have been several reviews. Dr. Inzucchi will actually be in Pittsburgh later this month and speaking at the Greater Pittsburgh Diabetes Club, plus our university-wide endocrine conference, but he takes care of a lot of people with diabetes. And he actually came up with some guidelines based on what's done in Canada, and Australia, and Europe, suggesting that it may very well be safe to use metformin in people with a EGFR of 45 to less than 60, with EGFR being a much better measure of renal function than serum creatinine alone.

We know that there are people who can have a creatinine of 1.1 and have an impaired EGFR. And other people who can have a creatinine of 1.6 and can have an EGFR that's fairly reasonable.

If the creatinine drops below 45-- and then this is where I also get nervous, and I'm not inclined to continue to use it-- not to initiate it, and perhaps to reduce the dose by 50% in somebody who is already on it. Now this is a study that actually was just recently published, and looked at the prevalence of metformin use in adults with type 2 diabetes according to age and CKD category.

So if we look, for purposes of this talk-- if we look at people at age greater than 65-- we'll just stay here to keep it easier. And these are categories of EGFR. So this would be greater than 90, greater than 45, and greater than 30. And then this would be very severe, where there's actually a person out here using metformin.

So it is being used in people. This is in the United States. Even though it doesn't look like an American author it is in the United States from the NHANES study. It is being used in people with lower EGFRs.

What the same group did, looking at the data, is they thought, what is the serum bicarbonate and what is the anion gap? Because the fear has always been lactic acidosis with use of metformin. And what they showed is as-- and they did look at this according to age as well, but there was a very complicated-- It would take me probably a good 10 minutes to walk you through it.

But just looking at it across CKD stage among all age groups, there was a-- wonder if I can get rid of that thing here. But there was a decline in serum bicarbonate that was a little bit lower in those on metformin compared to those not on metformin, or on non-metformin therapies.

There was also a difference in the anion gap. It was a little higher in the metformin users than in the not-metformin users. But the serum bicarb really didn't drop below 24, so it never really reached dangerous ranges. So the conclusions of these authors was that their findings supported a cautious expansion of metformin use in people with stage 3 CKD.

But they did say that we really don't have any studies of metformin in people with CKD to show that there's any cardiovascular benefit, and it needs to be clarified. But it does give some reassurance, at least gives me some reassurance for what I'm doing with my patients when I do continue metformin in people with EGFRs down to 45.

Metformin has similar efficacy in the elderly as in the non-elderly as shown by levels of HbA1c here. And interestingly enough, I'm going to be focusing a little bit on congestive heart failure with these next studies coming up. That the incidence of mortality in people with congestive heart failure, these are people-- and this is survival curves in people on sulfonylurea monotherapy. This is metformin monotherapy, and this would be combination metformin and sulfonylureas.

So metformin, in combination with the sulfonylurea, was associated with a lower mortality when compared to sulfonylurea users alone. I want to let you know this is not a randomized controlled clinical trial. This is a database study just looking at outcomes in people who were hospitalized with congestive heart failure. But in fact, it looks like metformin may have some protective effects on mortality in people with congestive heart failure, which is also very common in people with diabetes.

So speaking of congestive heart failure, we've all but stopped using the thiazolidinediones after all the controversy about rosiglitazone, and whether or not it caused an increase in cardiovascular events that hadn't been reported in the previously reported trials. So we'll just do another look at pioglitazone. I'm not advocating that you use pioglitazone, but this is the study that is hot off the press from yesterday in the *New England Journal of Medicine.*

Really, rosiglitazone, is all but not used. Pioglitazone, I will leave it to you. I'm still not a big fan. But this is the Ira's study, where this was a group of individuals who did not have diabetes at study entry. But they were enrolled in the study following a stroke, with the idea that insulin resistance is a risk factor for recurrent strokes in people at high risk for a stroke.

So the purpose of this study was to use pioglitazone to reduce the incidence of future strokes. And in fact, when they looked at the possibility of an event-free survival, there was a significantly improved event-free survival in the pioglitazone group compared to the placebo group. This was a multi-national study that was continued over now I think at least seven or eight years, with a mean duration of follow-up of five years.

So those subjects, the reduction in risk of a recurrent vascular event in those receiving pioglitazone was about a 24% risk reduction, and it did reach statistical significance. So there is an accompanying editorial that I think is a very well-written accompanying editorial, that actually congratulates the authors for this study, for carrying this study on during the whole thiazolidinedione controversy. But said, what do we do with these results?

And I think that this will probably be a topic of discussion over the coming months-- is yes, it did reduce the incidence of stroke or other vascular events in this high-risk population. It actually did reduce the incidence of diabetes in this high-risk population, but there was more weight gain.

So this is the percentage of subjects in each group gaining more than 4 and 1/2 kilograms during the study. And as you can see, that was higher with pioglitazone. This is something we know it does. There was more edema. And there were more bone fractures. So these are all things that we know.

So I would interpret these results cautiously, but it is provocative information. What about the newer agents? The dipeptidyl peptidase-4 inhibitors. There are now four of them available for use. Linagliptin does not require any dose adjustments for renal insufficiency. The rest of them do require some dose adjustment.

There are three very large clinical trials at the recommendation of the FDA. Any new drug that comes on the market has to be shown that there is no increase in cardiovascular events following the whole rosiglitazone fiasco.

And with the exception of saxagliptin, which showed a higher incidence of hospitalizations, actually a 27% increase in risk for hospitalizations for congestive heart failure, basically all of these were negative studies. There was no improvement in cardiovascular outcomes, and there was no increase in cardiovascular outcomes with any of these agents.

Some of the benefits of this particular class of agents, they're taken orally, they're once a day, they lower the A1C up to 1%, they have no effect on weight either gain or loss, the risk for hypoglycemia when not used with insulin or sulfonylureas is very low if not null. There are minimal GI side effects. Some of the more severe side effects are actually quite rare. Pancreatitis does not seem to be coming through to be much of an issue. And they can be used in combination with almost any other drug.

This was a meta analysis, again, just recently published in the *New England Journal,* that showed when a meta analysis was done of all the studies that included either the DPP 4 inhibitors, or the glucagon-like peptide-1 receptor agonists which are the injectable agents, that there was overall no effect on risk for heart failure. And the reason for why that occurred in the saxagliptin study is not entirely clear.

And I will finish up with this class of drugs. So this is the newest class of drugs, the sodium glucose transporter 2 inhibitors, that actually create symptoms of hyperglycemia while lowering the blood glucose. And there are now three that are on the market-- canaglifozin, dapaglifozin, and empaglifozin, with different dosing strategies.

What they do is they actually inhibit these transporters located at the proximal portion of the convoluted tubule, and prevent the reabsorption of glucose. So there is more glucosuria. And usually our kidney will not be able to reabsorb glucose once our glucose has reached a level of 180 to 200.

These block it at much lower levels of glucose. So they are effective agents at lowering the blood glucose. They do cause polyuria and polydipsia.

This is another study that is getting a lot of attention, because following the UKPDS which showed reductions in vascular events with metformin, this is now the only other study that is showing a reduction in vascular events with a diabetes medication. So these are subjects, these reductions in A1Cs in both arms of empaglifozin arms which were two different doses.

But compared to placebo, there were reductions in vascular events over time. In the interest of time I won't go through each of these slides, but you can see for yourself that empaglifozin was associated with more favorable outcomes. The primary outcome where there was truly a statistical difference was in hospitalizations and occurrence of congestive heart failure.

It is possibly easy to explain. There might be some myocardial remodeling, but these drugs are essentially diuretics, so it's like giving your patient a diuretic while you're lowering the glucose. So the side effects are polyuria, polydipsia, increased thirst. So use cautiously in the elderly who have an impaired thirst mechanism anyway. They can easily become volume depleted and dehydrated.

There is an increased risk for vulvovaginal candidiasis and genital infections. The genital infections are in both men and women, As well as an increase in risk for UTI in both men and women. You're creating an environment that bacteria like.

There is some increase in LDL cholesterol. This is not really as much of an issue. Again, there's no hypoglycemia when used alone or in combination with non-insulin secretagogue types of agents or insulin. There is some weight loss and reductions in blood pressure. They do act like diuretics. They are very, very expensive.

There have been reports of this syndrome of euglycemic diabetic ketoacidosis with these drugs. They have not all been in people with type 1 diabetes. Again, they lower the blood glucose, so someone may not be aware that they're developing DKA as they become ketotic. But the risk does not seem to be terribly high. This was just reviewed by the FDA in October.

High risk for volume depletion, hypotension, and dehydration. They do not work in the setting of CKD. The lower the EGFR the less likely they are to work. They depend on a near normal EGFR. And they are relatively new. We're still learning about these.

And then if we think about the elderly, this has not really been talked in the literature, but a lot of male patients here have BPH. And I think that just giving them a drug that fills their bladder more often might be causing problems down the line, but that is a personal statement in there.

So what do you do with what I've told you? Well, metformin I think is still your first agent. I'm not afraid to use it in people with moderate degrees of CKD. Following that, if your focus is on agents that don't cause hypoglycemia, and the patient has a good insurance plan to cover the costs of these agents, the DPP 4 inhibitors are a nice secondary addition.

The SGTL2 inhibitors, there are good agents, but there are reasons to use caution in the elderly. Not absolute contraindication but things to think about. And actually, the injectable GLP-1 receptor agonists are also useful.

So just to summarize, we know that type 2 diabetes is common. We know that life expectancy is increasing, so we will be seeing more and more of these patients that we have to think of all these things. Glycemic target should be individualized. I won't repeat that here.

We need more research in the older adult population. What is the safest, most effective regimen that people can afford is yet to be determined. Thank you for your attention.