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Transcript

Managing Diabetes in the Frail Multi-Morbid Patient

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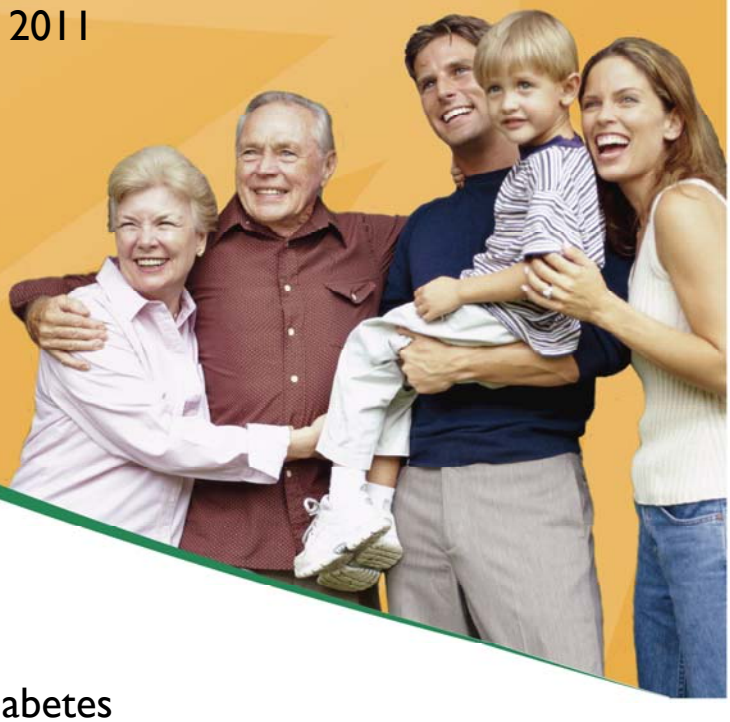

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We are fortunate to have three faculty with us today: Dr. Michael Fleming, Dr. Peter Boling, and Dr. John Buse. Dr. Fleming is chief medical officer for Amedysis Home Health Services. He is a clinical associate professor of family medicine at LSU Health Science Center in Shreveport, Louisiana, and clinical assistant professor of family and community medicine at Tulane University School of Medicine. Dr. Fleming has more than 30 years of medical field experience and is past president of the American Academy of Family Physicians and the Louisiana Academy of Family Physicians. He was also founding president of the Louisiana Health Quality Care Forum. Dr. Fleming also serves as chief medical officer at Antidote Education Company, as well as Amedysis. Dr. Fleming?

Michael Fleming: Thank you. Joining me today are Dr. Peter Boling and Dr. John Buse. Dr. Boling is the director of long-term care and geriatrics at the Virginia Commonwealth University Medical College of Virginia in Richmond, Virginia. Dr. Boling started the VCU House Calls Program in 1984, and has focused his career on care of the frail and vulnerable. He has had a particular interest in care coordination, care transitions, and home health care, an area of expertise in which he is recognized nationally. Dr. Boling has also authored a text, "The Physician's Role in Home Health Care."

Dr. Buse is a professor at the University of North Carolina School of Medicine in Chapel Hill, North Carolina, where he serves as the director of the Diabetes Care Center, chief of the division of Endocrinology and executive associate dean for Clinical Research. Dr. Buse has a diabetes practice located at UNC, as well as at the Salem Center in Winston-Salem, North Carolina. Dr. Buse has authored more than 200 publications and is involved in numerous multicenter clinical

trials. He is past president of the American Diabetes Association. In 2010, Dr. Buse was named Castle Connolly National Physician of the Year.

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Drs. Fleming and Boling have no relationships to disclose. Dr. Buse's disclosures are shown here on this slide. Dr. Fleming?

Michael Fleming: Upon completion of this activity, participants should be able to discuss the outcomes of recent studies describing the ineffectiveness of tight control protocols in managing diabetes for frail populations.

Dr. Buse will begin our presentation with a review of the updated recommendation for diabetes care in the elderly. Dr. Boling will then discuss how to incorporate these recommendations into everyday practice. We will then have a question-and-answer session where the faculty will address any questions that you have. Simply type your question in the question box located in the left-hand lower side of the player window. Dr. Buse, I'll now turn it over to you.

John Buse: Thank you very much. So, what I will go over today is first just a bit about glycemic targets and the evolution in thinking in a post-ACCORD world. Secondly, touch on the very important issue of the need to distinguish between type 1 and type 2 diabetes. Now we know that there are lots of kids who get type 2 diabetes, and we also know that the vast majority of people with type 1 diabetes in America are actually adults. And thirdly and most importantly, talk about new studies that relate to paradigms of how to achieve glycemic control.

So, the first topic is the glycemic targets and, as you know, before the DCCT trial, back in the 1980s, the American Diabetes Association established a glycemic goal of an A1c of less than 7%. The DCCT was the first evidence that that was a reasonable target. That was conducted in generally younger patients with type 1 diabetes, and we'll go over some more data in that regard in a moment.

Years later the American College of Endocrinology, and in fact virtually every august body in medicine adopted the A1c target of less than 6.5%, though no clinical trial ever achieved an A1c of less than 6.5%. The way I tend to talk to patients about these targets is that we'd like to get the A1c as low as possible without unacceptable adverse events, and that might be a side effect of therapy

-- hypoglycemia, weight gain being the two most common. Or it could be an unduly complicated medical regimen or more expense than they can handle.

And that if we were to translate that number of an A1c less than 7 into glucose monitoring targets, in general blood sugar of around 100 would get you an A1c of less than 7%. And I don't tend to encourage people to check postprandial glucoses, but what I tell them is if they do check their blood sugars other than before meals, they should see blood sugars less than 200 most of the time.

These are summaries of the older clinical trials looking at the effect of lowering glucose as assessed by hemoglobin A1c on the incidents of complications. And I mentioned the DCCT before. Generally younger patients with type 1 diabetes average duration of disease of about six years. The KUMAMOTO study was a study in Japan involving patients who had type 2 diabetes but no evidence of metabolic syndrome or cardiovascular risk, so they couldn't have hypertension, they couldn't be overweight. Very unusual population of type 2 diabetes.

And the UKPDS, which you all know well, is a study of new onset patients with type 2 diabetes conducted in the United Kingdom.

In all three of the trials they achieved an A1c of around 7% overall in the intensively treated group, and the comparison group had an A1c of 8 in the UKPDS and 9 in the other two trials. And what you can see is that there was a substantial reduction in retinopathy, nephropathy and neuropathy in all trials in which they were evaluated. And that works out to about 20% to 30% reduction in risk for every 1% reduction in hemoglobin A1c.

The DCCT had trends towards improved cardiovascular outcomes which didn't even come close to being statistically significant because there were so few events. And the UK PDS demonstrated a 16% reduction that just missed statistical significance with a p-value of 0.052.

Now, these are some of the curves which I think are the really important learning for this particular discussion that we are having about management in the frail elderly. And that is that in the DCCT, and there are similar data from the other trials, they developed these nice curves showing the relationship of the rate of progression of complications as a function of A1c and time. And the important point is that it takes years for a change in A1c or a difference in A1c to express itself as an increased risk of complications, particularly when you look at patients who have A1c in the 8%, 7% and lower range.

And so, though there might be an argument to more intensively manage patients who have an A1c of 9%, 10%, 11%, particularly in the frail, advanced elderly where life expectancy is a major limitation, an A1c of 8% or less clearly is adequate in that population.

On the other hand, in a patient in their forties with new onset disease, there might be a clear rationale for aiming for an A1c of even less than 6%, where

there is plenty of time for modest differences in rates of complications to make a difference.

This next slide looks at the recent clinical trials, so that is the ACCORD study, the ADVANCE study, and the VA diabetes trials. ACCORD and ADVANCE, very large studies, over 10,000 patients. The VA, a smaller study. ACCORD and the VA study aiming for A1c of less than 6, and in the ADVANCE trial less than 6.5%.

So, all three studies really look to answer the question, does treatment of diabetes beyond the current guideline of less than 7% A1c provide for additional benefit? And what you can see is in the blue line, from a baseline A1c of between 7.5% and 9.4%, in each of these about a 1% to 1.5% reduction in A1c was associated with no statistically significant benefit with regards to cardiovascular events. And specifically in ACCORD, there was a nominally or arguably statistically significant increase in mortality associated with this more intensive treatment.

So, what we would say is there is no support from the point of view of cardiovascular endpoints in pursuing more aggressive targets than the standard target of an A1c of less than 7 in patients who are middle-aged and older who are already at high risk for cardiovascular disease or have clinical cardiovascular disease, and there is some evidence of potential harm.

This slide is one of the microvascular outcomes from the ACCORD study, and this is designed to mirror the microvascular outcomes of the UKPDS study, the best or biggest trial in type 2 diabetes. And I just show you this to point out that if you look at clinically important microvascular endpoints for patients, like the development of renal failure or requiring laser therapy of their eyes or vitrectomy, or the development of clinical neuropathy, there really was no benefit for the more intensive treatment in ACCORD on these clinically meaningful outcomes.

So, the story that I've been trying to develop here is that there is not a great deal of benefit that we can establish in older patients with type 2 diabetes at high risk of cardiovascular disease or with preexisting cardiovascular disease.

Now, the other issue is their harm in approaching lower levels of A1c. And because I think virtually everyone on the line probably treats patients in their eighties who are frail and unlikely to live three to five years, and treats patients in their forties who are likely to live 40 or 50 years, I think it's very important not to get confused about what ACCORD really tells us.

So, ACCORD tells us there is no benefit from more intensive therapy, but is there harm? And this is a very important analysis where they look at the hazard ratio for mortality as a function of A1c on the Y axis, the intensive group being in orange and the standard group in blue. And what you can see is that under an A1c of 7%, where that arrow is, there really is no excess mortality associated with intensive treatment.

So, the people who had excess mortality in ACCORD where the patients who were in the intensive treatment group and whose doctors and the patient themselves were aiming for an A1c of less than 6, but still had an A1c of over 7%.

So, if there is this disconnect between how intensively you are treating a patient and how well they are responding to that treatment, that is a sign that there may be trouble looming ahead, and really working on adherence or perhaps thinking about alternative approaches to reducing cardiovascular risk would be more appropriate.

But the point really is that if you have a patient who has an A1c of 6% or even less, and there has not been a -- there are no substantial adverse effects from the therapy, the best evidence from ACCORD is that that is not associated with excess mortality.

So, the next topic is to touch on this issue of type 1 versus type 2 diabetes, and it is getting to be tough now to tell the difference. Let's say in an obese 14-year-old child, is that really going to be type 1 or type 2 diabetes? There are features of each. Or in the frail elderly, where frankly most people with type 2 diabetes are thought to have had insulin resistance for their entire life and therefore classically, at least in the past, were dying of heart attacks in their sixties and seventies. And so when you see an 80-year-old with diabetes, it needs to tweak your Spidey sense that maybe this isn't run-of-the-mill type 2 diabetes.

The importance is in the first line with regards to treatment. In type 1 diabetes, insulin is the therapy. Nothing else really provides substantial benefit. And the regimens that are associated with reasonable levels of glycemic control without problems with severe hypoglycemia are these relatively complicated multiple daily injection regimens. Whereas, in type 2 diabetes, in general the end stage of therapy is the combination of oral agents and insulin.

We used to call type 1 diabetes, juvenile onset diabetes, and type 2 diabetes, adult onset diabetes, but we know that 10% of adults with a new diagnosis of diabetes. So, you have a 70-year-old man in your office that you've just diagnosed with diabetes, 10% of them have a slowly evolving form of type 1 diabetes, not type 2 diabetes. And we know now that at least 10% of children have type 2 diabetes.

Classically, type 1 diabetes was associated with thinness, people that were less heavy than average, and type 2 diabetes with obesity, but we now know that 20% of type 1 diabetics are obese and 10% of type 2 diabetics are thin.

Family history can be positive or negative in either -- 10% of type 1 diabetes patients have a close relative, though the majority of patients with type 2 diabetes and diabetic ketoacidosis, which used to be the defining characteristic of type 1 diabetes, and it is more common for a patient with type 1 diabetes to

develop DKA in their lifetime than a patient with type 2 diabetes to develop DKA in their lifetime. But because there are so many more patients with type 2 diabetes, in fact, of all the DKA in America now, at least half is in patients with type 2 diabetes. So, under severe stress, patients with type 2 diabetes can develop DKA.

I think the best clinical characteristic of type 1 diabetes is that the blood sugars tend to be extremely variable. On the same day you could have a blood sugar of 40 and 400, and people tend to have problems with big time hypoglycemia, severe hypoglycemia. Whereas, type 2 diabetes, the blood sugars could be high all the time or they could be intermediate all the time, but they tend not to go from 40 to 400. They are so insulin resistant, it is actually pretty hard to push their blood sugars around very fast and they tend to have less trouble with severe hypoglycemia.

As you know, type 1 diabetes is associated with other autoimmune conditions, the most common being thyroid disease, and it's always worthwhile to remember if you have an insulin-treated patient that is not feeling well, to remember that list of other autoimmune diseases, which is incredibly broad, including Addison's disease and autoimmune hepatitis, and B-12 deficiency.

So, the test that you can use early in the course of diabetes is the anti-GAD antibodies and other antibodies to distinguish type 1 from type 2 diabetes. But remember that these antibodies are only present in about 70% of people. The antibodies almost never -- 70% of people with type 1 diabetes.

Later in the course of the disease, which is usually what we're talking about in the elderly patient, in type 1 diabetes a C-peptide should certainly be at the lower limits of normal or frankly low or generally zero. In type 2 diabetes late, you might see a low normal value, but almost never would you see a zero value. And I think it's important to distinguish the two forms of diabetes particularly in the advanced elderly.

So, if we go to case No. 1, and I'll ask you a question about it in a second. It's a 78-year-old nursing home resident who presents for evaluation of recurrent episodes of severe hypoglycemia. She was diagnosed at age 65 during a routine insurance exam. She takes a combination of 70/30 insulin, glargine and sulfonylurea. Not the most standard approach, but that's what she and her primary care doctor worked out. She is checking her blood sugars four to six times a day. She lives in an assisted living facility. And the levels range from the 30s to the mid-500s over the last two weeks. These episodes of severe hypoglycemia usually in the afternoon or early morning. The average on her meter is 196, and when you download it, the standard deviation is 130. So, she's got plenty of readings in the 40s, 50s and 60s, and plenty of readings in the near 400 range.

Her past medical history is otherwise unremarkable and she doesn't have any family history of vascular disease. She doesn't use tobacco or alcohol. She is

5'1" and weighs 98 pounds. Blood pressure and pulse and the rest of her exam is normal. And you can see her laboratories; her A1c is pretty high at 8.6. Her lipids are very normal and her creatinine is fairly normal for age, but her estimated GFR is probably on the order of 40 or so.

So, the question is, what diagnosis code would you use in evaluating this patient? Would you use a code for type 2 diabetes, type 1 diabetes, secondary diabetes, gestational diabetes, or other abnormal glucose, or none of the above? And please enter your answer, if you can.

All right. Well, the answer is that this is a case of type 1 diabetes. We measured a C-peptide, it was basically zero. She had diabetes a long time, so the utility of the antibody test would be diminished for having longstanding diabetes. But the point really is, when you have these frail, elderly people with ballistic blood sugars, think that they might have type 1 diabetes and they may need a more sophisticated regimen than the standard 70/30 insulin-based regimen.

So, let's talk a bit about glycemic control and how to get it accomplished. This slide explains the design of the so-called 1-2-3 study, where patients came in on two or three oral agents, and they were treated with insulin glargine, aiming to get the A1c to less than 7%. If they were more than 7% after 14 weeks, they got randomized to one additional injection, or two additional injections, or three additional injections of a rapid-acting insulin analog called insulin glulisine.

Here you see the overall results, so the 37% of the patients achieved an A1c of less than 7% with glargine during the run-in. So, glargine very effective treatment to lower A1c in patients with type 2 diabetes. And then you can see an additional 23% got to an A1c of less than 7% when they had glulisine added. But what you can see on the right is that, in fact, whether people took one, two or three additional injections of glulisine, it didn't make a big difference in the end A1c achieved.

So, though the standard recommendation is to go from one to two to three to four injections a day of insulin, we need to be very careful that as we do that we are actually achieving better outcomes. In fact, in this study the patients that got two and three injections of glulisine had an increased risk of hypoglycemia and weight gain.

The second study I wanted to show you is the so-called GWCO study. It was published in the *Annals of Internal Medicine* earlier this year, and this used a combination of glargine, arguably the most effective technique, basal insulin for lowering fasting glucose, with exenatide, a GLP-1 receptor agonist that really works mostly in the postprandial state.

So, the most powerful fasting approach, glargine with arguably one of the more powerful postprandial approach is exenatide. As you know, exenatide is generally associated with weight loss and no increased risk of hypoglycemia, so we hypothesize that this combination of glargine and exenatide might show

benefits in a way that we didn't see in the prior study adding rapid-acting insulin to glargine.

What you see here is that the patients that had -- were randomized to get placebo twice a day, in addition to having their glargine dose optimized, they only lowered their A1c to 7.4%. Whereas, the patients that got exenatide twice a day, in addition to optimized glargines, they got their A1c down to 6.7%, a rather remarkable achievement in patients with longstanding diabetes who were already failing glargine plus oral agents.

With regards to safety, you can see that the risk of hypoglycemia was essentially identical between the two arms. There were the typical GI adverse events that we see often with these GLP-1 receptor agonists.

So, if we take these two new studies and we apply them to this ADA EASD algorithm, which is classically recommended at diagnosis, people with good lifestyle on metformin, the step two therapies that are recommended are basal insulin, sulfonylurea, pioglitazone or GLP-1 receptor agonist. Where do we go from here in deciding how to modify this algorithm?

Well, the first thing we know is if we use sulfonylurea, it tends to accelerate secondary failure. They are the cheapest agents around, they are certainly fair game, but it does make it more likely that patients will end up on insulin therapy in the near term.

Now, frankly, in the advanced elderly, I don't have a huge objection to using sulfonylureas, because we don't -- we're not that concerned about accelerating their future need for insulin. But it can cause hypoglycemia, though the risk of hypoglycemia is not dramatically altered in the elderly compared to nonelderly subjects. If you can avoid hypoglycemia, that clearly might be a good thing.

Pioglitazone has developed a lot of baggage about heart failure, and particularly in the elderly, heart failure and edema are issues. On the other hand, in the elderly, if they are losing weight, there might be some disadvantages to pioglitazone as a technique to mitigate that. But some of the shine has rubbed off the glitazones with regard to the therapy of type 2 diabetes. And I just showed you the study that intensive insulin does not really provide a great deal of benefit beyond that achieved with adding insulin glargine.

And so perhaps an alternative approach, though not approved by the FDA, it's under review by the FDA, is the combination of insulin and GLP-1 receptor agonist. Now, specifically it has not been studied in the elderly.

This chart reviews some of the issues with each of the classes of medications. I'm sure at some level you are aware, though, maybe you haven't ever counted them up, but there are about 14 different approaches that we can use for the treatment of diabetes. The classic ones are at the top that have been around for years and years. But the newer ones are at the bottom and generating a lot

of interest because they're not associated with hypoglycemia and they are generally associated with either weight loss or they are neutral with regards to weight.

They do have adverse effects that I want to just touch on very briefly that are common, and I think the ones that you have to be careful with, particularly in the elderly, are with metformin, not using it in patients with advanced renal disease as determined by estimated GFR. Remember, it can cause B-12 deficiency, so you may want to screen for that.

With pioglitazone, we have touched on the issues of heart failure and bone fractures, particularly in women. The only issue that is left on this slide with regards to adverse effects, it's a real issue. Others are concerns, but issues where the evidence base that it's a real clinical problem is rather modest. But exenatide is cleared by the kidney, and in patients with advanced renal disease, CKD stage 4 and 5, it is associated with a high rate of nausea, vomiting, which could cause acute or chronic renal failure related to dehydration.

So, to summarize, in managing diabetes in the frail, multi-morbid patient, my advice would be to be flexible with regards to targets. Generally, I think the A1c target of less than 7% is appropriate in the general population, but in the frail elderly there are unlikely any adverse consequences over the intermediate term of having an A1c of closer to 8%.

You have to back off therapy for hypoglycemia and other adverse effects. And in particular I would avoid these multiple daily injection therapies as a matter of routine, which is often recommended by endocrinologists except in the setting of significant insulin deficiency, like type 1 diabetes or latent autoimmune diabetes of adults, which is really present in 10% of adults. And particularly the advanced elderly are at high risk for this type 1 diabetes condition, and to consider novel agents which are not associated with hypoglycemia as an alternative. So, thank you very much, and I'll turn it back over to Michael.

Michael Fleming: Great. Thanks, John. Peter, tell us how we put these recommendations into practice.

Peter Boling: Yes, sir. Good morning or good afternoon to everybody on the line. I'm a geriatrician and so my perspective is going to be that of a person that is concentrated primarily on care of people with advanced chronic illness, and I'm going to tell you what I mean by that.

But to start off, let's look at a case, and this is modified from real world practice of mine, a nursing home patient. A 79-year-old woman with coronary artery disease, advanced kidney disease, diabetes, peripheral vascular disease, osteoarthritis, and mild cognitive impairment. You can see that she has limitations in several activities of daily living. She had been in the hospital with acute coronary syndrome and a non-STEMI, and had stents placed and had

come out of the hospital on recommended therapies for her medical conditions, including her heart and endocrine problems.

Included in that regimen was a very intensive protocol for maintaining near euglycemia with sliding scale recommendations beginning at blood sugar of 126 and administered four times a day.

The A1c before hospitalization, 8.5%. You can see her vital signs are normal, her blood pressure actually a little low when standing up, and she was not doing very well. She was weak and tired, progressing slowly in rehab. I guess this was actually after she came out of the nursing home to home health, and this was ascribed to her heart disease.

So, the things I want to start with are understanding your population. And I think this is a very important distinction, because what I'm going to tell you in the main part of my presentation is going to be about caring for people who don't have very much time left. And I would approach a 50-year-old relatively healthy patient, or a 60-year-old, even 70- or 80-year-old patient with a very good sort of protoplasm very differently from how I approach frail elders.

So, first thing to know is who are your patients, how old and what their prognosis. And then I think we need to look at the clinical trials and see if the clinical trial results that we have been looking at are really applicable to the patient population. That will then lead you, I think, to be able to conclude what sorts of results are reasonable to seek in your patients.

So, ways of figuring out how healthy our population is in geriatrics tend to track back to ADLs, and I'm going to spend a couple of minutes talking about ADLs. You can see here on the bottom left a standard picture of older folks walking in the woods, and on the right an actual house call patient who perhaps is more characteristic of the people that I'm talking about in my presentation.

If you look at the patients who have been admitted to Medicare Part A home health, this is 2007 data, you can see from this slide that they are really pretty old. Almost 70% are above age 65 and, in fact, more than half are above age 75, so it's a very old population. And now let's look at their functional status.

These are, again, national data showing that half of the patients have deficits in four or five activities of daily living, and that sounds pretty grim. That sounds like an extremely debilitated population. So, the next slide helps clarify that a little bit in that only 20% of the patients actually need human help with four or five ADLs, but there are about half of the patients that need human help with at least one ADL. This is actually a fairly impaired population.

This slide is from a life table analysis looking again at an aged population and applying the general degree of health or illness to understanding prognosis. So, if you take, for example, the collection of three bars at age 80, these are older women, those in the top quartile, the healthiest of those ladies on average are

going to live about 13 years, compared to those in the bottom quartile who perhaps have four or five years left to live.

And if you start thinking about your population in this way, you can perhaps gauge which of your 80-year-old patients you want to push hard to attain better glycemic control. And this is the same analysis for men, which has essentially the same result.

Now I'm going to shift to another approach, because you can't really do a life table analysis very easily in your office practice, but it may be possible to apply gait speed as a way of figuring out who is going to live longer. And this is a comparison looking at age across the X-axis, from 65 to 95, and survival on the Y-axis as connected to the gait speed.

So, the top green bar, the top green line is a person that can walk 1.5 meters per second at age 65, and down here, when you get to be 85 perhaps can walk about 4 or 5 meters per second, as compared to somebody at the bottom of the histogram who is much slower in their walking speed, and the resulting life expectancy associated with just looking at the population health characteristics is down to about five years. So, gait speed might be a way of getting a proxy on how long your patients are likely to live. And this is basically the same diagram for older men, to be complete and inclusive.

With that background and, therefore thinking about a frail, elderly population, I want to go to the literature on diabetes and see whether this literature really applies to these types of patients and, if so, how we can use it. I'm going to concentrate primarily on ACCORD and ADVANCE, which Dr. Buse has already mentioned. And I will just, at the closing, point out a couple of things about the clinical trials that have been published on exenatide, which is an exciting new agent in diabetic care.

So, reminding you again, think about who are your patients and whether those clinical trials apply to them. Would the patient that you're seeing today have been included in the clinical trials, for one thing? So, is it reasonable to apply the results of those trials to that patient, and then do the results of the trial connected with the patient's comorbidity and life expectancy alter your thinking?

So, first thing about ACCORD. It is a trial of type 2 diabetics, a randomized controlled clinical trial of over 5,000 patients per group, so quite large. They had to have some cardiovascular disease or cardiovascular disease risk factors to enter, and you can see the age range of 40 to 79, but, importantly, the mean age of 62. So, this was not a study of old, old people, although there were a few older patients in there, age 79. To get in you couldn't be ultra-frail and their glycated hemoglobin had to be 7.5% or more to enter.

You can see the metabolic controlled targets as discussed by Dr. Buse. It was a moderate improvement down to, ideally, down to 6.5%, but in most cases down towards about 7%.

This slide shows you, in a very sort overarching view, the main results. And the graphs are too small to actually see up close, and I'm going to show you a couple of them up close in a minute. But I want to call to your attention the fact that the orange and blue lines, which are the two groups -- the usual care group and the intensive care group -- are almost exactly superimposed in all of these outcomes which have to do with both cardiovascular endpoints, death and microvascular complications. That's the overarching, big sky view.

We'll go in a little bit closer and look at heart attack or death. And, again, the point is, the main point, they are essentially the same comparing the intervention group to the control group.

This is all-cause mortality, and as Dr. Buse explained, there was a slight difference. Actually, if you look at the numbers, a 20% increase in mortality, although just barely inside the statistical confidence intervals, and probably associated with some anomalies in terms of the types of patients included. So, let's say for the sake of argument that the risk of dying was the same, the main point is there was no improvement in the likelihood of dying.

To refine the analysis, folks have done a multivariable approach. And if those of you on the line are not familiar with multivariable modeling, the basic idea here is along each of the rows we are looking at a particular outcome or endpoint. And there is a line drawn in the middle. If the little central black dot is to the left side of the line, that would tend to indicate improvement; and to the right of the line would tend to indicate the more intensive treatment was worse. The little horizontal line through the black dot tells you if the difference is statistically significant. So, if that little black line crosses the middle vertical line, then that tells you it is not statistically significant.

So, in this analysis there is a slight improvement in the odds of having a myocardial infarction with the intensive treatment, but there was also a slight increase in the risk of dying as part of the intensive treatment group.

I'm going to switch gears now and talk about the other large recent randomized control clinical trial of type 2 diabetic patients. Again, people with cardiovascular risk factors, over 5,500 per group. Again, a randomized control clinical trial with a mean age of 66 plus or minus 6. So, not an old, old group. The intensive group had baseline A1c of 7.5% being pushed down to 6.5%, and the standard therapy group started at 7.5%, ended up at 7.3%.

I highlighted the incidents of severe hypoglycemia as one of the adverse outcomes, and it was about twice as high in the intensive control group, which conforms to my experience in clinical practice.

The next slide again shows you the overall outcomes, and I showed the lines at a fairly microscopic view just to give you the feeling that there is not much difference between the intensive control and the standard control regimen.

On the bottom left, I highlighted that there is actually a slight difference with favoring intensive control and, as Dr. Buse pointed out, in the incidents of microvascular events, particularly retinopathy. And retinopathy is important to older patients because it has to do with how well you can see. But I also pointed out that it's about a 2% absolute difference in improvement in outcomes after a period of almost five years of treatment. So, a pretty small benefit for a few patients with a large number needed to treat after a relatively long period of intensive regimen at the end of life.

This is a meta-analysis applied to ADVANCE, and again showing that there is really little difference between the intensive group and the standard group on almost any of the outcomes with the exception of kidney problems, which is a microvascular issue. And in this case about 60 of 11,000 people would have benefited from the intensive control, looking at that particular outcome.

Closer-up look at heart attacks and cardiac death with ADVANCE showing no difference. And this is a microvascular event up close, so you can again see that small statistically significant but really modest improvement in microvascular outcomes at the end of about five years. And, finally, death really not improved.

Now, I am going to shift over and talk briefly about the published studies on exenatide just very briefly. Not to explain the merits of the drug therapy or to necessarily argue with the approach that Dr. Buse presented in terms of the advancement of the science of diabetes care, because there certainly are some benefits to this approach. However, as you think about your 85-year-old home care patients, I have to question whether a bunch of studies that I'm going to show you here where the average age of enrolled patients is 55 to 57 years, applies equally well to the population we're serving in home care.

So, this was one study with a mean age of 55. This was the second study. You can't see the mean age as well, but it's 57 across all four groups.

This study was using exenatide versus premixed insulin 70/30 and metformin treated patients with type 2 diabetes. You can see there was some improvement in the glycemic control; however, the mean age of the patient is 57 plus or minus 10 years.

And, finally, in DURATION-5, exenatide once weekly resulted in greater improvements in glycemic control. Again, good in advancing the science, but mean age of 56.

As Dr. Buse mentioned, as we start using new drugs, we have to take into account the scientific merits and the improvements that they produce in terms

of clinical management, as well as other factors, which include side effects. So, exenatide does have a fairly significant degree of side-effect inducement, I guess, in patients -- nausea, vomiting, diarrhea being the most common. And then a variety of others quite strikingly more so than placebo.

And as is the case with many new therapies, this particular one, if you go to drugstore.com and check out the price, it is fairly expensive. So, you have to question, I guess, the merits of purchasing drugs that are that costly if you don't have a really strong gain in benefits.

So, one of the challenges, for those of us in geriatrics, is finding studies that are going to guide our management of patients that have significant chronic illnesses such as diabetes when there are relatively few older patients in the clinical trials. And having done some work with clinical trials, but nowhere near as much as Dr. Buse has done, I can tell you that there are a number of reasons why it's hard to get people into those trials. Physiologically, there are a number of changes that take place in the way that drugs are distributed in the body and are cleared particularly from the renal system and also potentially the hepatic system, which result in safety issues.

Older, more frail patients sometimes choose not to involve themselves in clinical trials, or their families may not unless they are particularly sure of what they might gain from it, and oftentimes are excluded on the basis of their comorbidities.

There were actually a couple of trials in the literature that I was able to find where really tight control of diabetes did produce some improvements in outcomes. For example, there were two studies looking at ICU-based care of patients, primarily cardiothoracic surgery patients, where they had hour-by-hour adjustments to their glycemic regimen. And with that actually had a significant and fairly impressive improvement in the clinical outcomes, particularly death, in that case, which is a very important outcome, and possibly deep tissue infections.

In general, however, setting that aside and looking at the hospital environment where a lot of the newly developed intensive regimens appeared to enter my life in terms of my patients being started on these protocols, there is very little evidence of improvement in surgical outcomes, wound healing, infections, or other types of important results that we would look to in terms of our patients.

So, I'm going to give you a somewhat different view of the bottom line. I actually am not exactly a nihilist, but approaching a nihilist when it comes to managing the diabetic care of my older patients whose life expectancy is two, three, four, five years. I don't think that we're going to help them by tight control, so I look for asymptomatic patients, which for me means not having blood sugars under 100, and not too often having blood sugars over 250. That means they won't have polyuria or blurred vision, and they will never have hypoglycemia. Their life expectancy is short. The process of care to get

intensive tight control is burdensome, it's relatively expensive. It's dangerous, potentially doubling the frequency of hypoglycemic events. It doesn't improve any of the important outcomes that we've looked at with the possible exception in selected patients, and relatively few selected patients of reduced retinopathy and nephropathy. And I think that A1c of 8% is a reasonable goal, but I actually am perfectly fine if I see 8.5% in my older patients.

So, in general, my recommendations and my approach is no short-acting agents after dinnertime. I see that coming out of the hospitals a lot, and my rationale there is that if you give a short-acting agent in the evening, it's too often the case that people become hypoglycemic after they've gone to bed, and particularly in some settings it is not easily recognized.

In general, I try not to give my patients regimens that involve taking medicines or checking their blood sugar more than twice a day, and I emphasize avoiding extremes. So, if I see a blood sugar under 100, then I see that as a potentially risky situation for an older person, because it's just one missed meal between that person and a serious significant hypoglycemic event, which can cause brain damage.

I think about the renal tubular threshold for excreting glucose into the urine and causing hyper- -- well, causing frequent urination. And I try to keep their blood sugars down low enough where they're not going to be having glycosuria, which would then induce diuresis.

I remind all of us that one of the guiding principles in medicine is to first do no harm, particularly if the therapies that you have to offer don't do much good.

Michael Fleming: Thank you, Peter. So, some questions, and this question from me. John, your comments on particularly Peter's bottom line?

John Buse: You know, I think we basically agree. I mean, particularly for the kinds of patients that he had pictures of. You know, basically, almost more about patient in the nursing home. There is nothing to be gained from intensive diabetes management.

I usually think of the renal threshold for glycosuria around 180, so I generally try and keep people's blood sugars under 200. I just don't want them getting up in the middle of the night and slipping in their own urine if they're incontinent. But I think we basically agree.

I think it's also important to realize, if you look back at that table with all the green and yellow and red boxes -- let's see if I can get the number. It's slide 33. There are a number of agents that are not associated with hypoglycemia now, and that is an alternative approach to use. But I think in general we agree.

Michael Fleming: Great. One question that came in and, John, I'll direct this to you. Why is it recommended not to check postprandial sugars?

John Buse: Well, I think there are two reasons. One, the primary safety issue in diabetes treatments is hypoglycemia, as Peter really highlighted. And you know nothing about hypoglycemia if you're checking in the postprandial period. So, you need to do the preprandial monitoring to evaluate patients for risk of hypoglycemia.

And, frankly, there has never been a study that showed that postprandial glucose monitoring is associated with better outcomes. It is something that was kind of concocted, I think, by the meter manufacturers to sell more strips, and there are some of the drug companies that propose that their agents really target postprandial glucose in the absence of lowering fasting glucose, and that that was an advantage. I think some of the shine has worn off those concepts.

Michael Fleming: Okay. And, Peter, sort of on the same topic, how often, in your patient, as you depicted here, in an elderly, frail patient who is at home and has to do their blood sugars themselves, how often do you usually recommend that they check their preprandial blood sugar?

Peter Boling: Well, I find that the two most useful times for me are before breakfast and before supper. And the rationale there is that before breakfast is when you're going to learn most about the overnight hypoglycemic risk. And I am interested in before supper because usually during the middle part of the day is when our older patients get the bulk of their glycemic load, and that is when we're going to see the greater extremes of hyperglycemia as a rule.

So, I am interested in those two times, but I will tell you that my old, old patients, as a rule, really don't like puncturing themselves, and so I'll give them a fair amount of slack on that. I ask them to check -- you know, rotate, so take morning sugars some days and late afternoon sugars other days. I find that unless the people are really compulsive or their families are very compulsive, we usually get a few data points each week. But rarely do I see old, old patients bringing me data even once a day, and usually not 14 readings a week.

John Buse: This is John. I agree completely, and I would go further that I think the most important thing is for them to check fasting and then particularly to check whenever they have symptoms. Because a lot of people will have that sort of weak feeling that Peter described in his case and not have the classic sweating, tachycardia, shaking kind of feeling. So, I think it's important for people to check whenever they feel unwell.

Michael Fleming: Yes. John, for a newly diagnosed 60-year-old diabetic with an A1c of 9.2% and polyuria, would it be reasonable to start, say, Lantus and metformin as first line?

John Buse: This is John. My preference would be just to start metformin and lifestyle intervention. This is not a call 9-1-1 problem. You know, have people self-titrate from 500 mg once a day to 500 twice a day to 1,500 to 2,000 as tolerated. Have them come back in a week -- I mean, have them come back in a month and see what their blood sugars are and then decide whether it's time to

add another agent. I think starting two agents at the same time is just usually not necessary.

Michael Fleming: Okay. Peter, any comment on that?

Peter Boling: No, I agree, and I use metformin a fair amount. One of the dilemmas we have with metformin, if the question about the degree of risk associated with the lactic acidosis, which is certainly a real deal. Although it took me about 10 years to find somebody who had actually seen a case. I know they occur, and with older patients that have renal impairment or heart failure, or liver disease, and it may even be occult liver disease, they are at greater risk of that very serious complication.

So, I do use a fair amount of metformin as an agent, and even in the old, old population with those cautions in mind. And will also remind the listeners that metformin, though it's not often talked about in this way, in my experience has a more frequent cause of GI side effects, particularly gas and even diarrhea, sort of distention in diarrhea than I was originally taught to think about. So, I think it's 10% or 15% of my patients probably in the end don't tolerate metformin because of the GI aspects of the medicine.

Michael Fleming: John, your comments on tolerance of metformin, because as in practice I actually did have an experience with a patient with the lactic acidosis. Your thoughts on that?

John Buse: So, there are pretty good studies now. Lactic acidosis occurs in the general population. It occurs in people with heart failure, renal failure and liver failure more so than other people. So, those are really risk factors for the development of lactic acidosis.

There are now studies in pharmacoepidemiologic studies in millions and millions of people, where they just can't find a signal for lactic acidosis. That said, there is a clear reason why, if you had chronic renal insufficiency your metformin levels and your circulation would be a lot higher. And so I think the European and Pacific nations' recommendations are to not use it at all in people with an estimated GFR less than 30, and to use it with caution and at lower doses in people with a GFR between 30 and 50. And I think that's entirely reasonable.

As far as the adverse effects go, I think even in the package insert, it's about 5% of patients will not tolerate the drug at all. I'd say another 5% to 10%, you have to coach them through it. I mean, you have to ask them to kind of tough it out a bit. So, Peter is exactly on target in that regard.

Michael Fleming: Great. Well, gentlemen, we've come to the end of our hour together, and I want to thank both of you for presenting to us today. I think this has been compelling, and I hope that for our audience that this has been helpful in the way you practice, particularly in this population of patients.

For all of you that have joined us, I want to thank you for participating in today's seminar. Please take a moment to answer the questions that will pop up just after we finish. Upon successful completion of this post-test, your certificate will be displayed and available for download in PDF format.

We hope that all of you look forward to future CME webinars that will be presented on clinical topics, and we hope that you all have a good day. Thank you.