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### Dissecting Clinical Trial Data from the 81<sup>st</sup> Scientific Sessions

Dr. Anderson:

The 81<sup>st</sup> Scientific Session presented by the American Diabetes Association were held virtually once again this year, exploring a range of topics from chronic complications to islet biology and everything in between. Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Anderson and joining me to discuss highlights from this year's session are two of my fellow hosts of *Diabetes Discourse*, Dr. John Buse, and Dr. Carol Wysham.

John, would you like to introduce yourself?

Dr. Buse:

Yes. I'm a Professor of Medicine at the University of North Carolina in Chapel Hill and the Division Chief of Endocrinology.

Dr. Anderson:

Thank you, and Carol, would you like to tell us a little bit about yourself?

Dr. Wysham:

Yeah, so I'm Dr. Carol Wysham. I'm a Clinical Professor of Medicine at the University of Washington School of Medicine and a Clinical Endocrinologist and Clinical Trialist at MultiCare Rockwood Clinic in Spokane, Washington.

Dr. Anderson:

Well, that's great. Thank you both for being with us, today. Let's start our discussion by talking a little bit about Scientific Sessions. And Carol, I'm gonna let you start off with what you thought might've been interesting at the Scientific Sessions.

Dr. Wysham:

So, I think most of my interest was in the really clinically relevant areas and specifically some of the larger clinical trials that were reported. One that I was most anxious to hear the results of was the GRADE study. And as your audience may or may not know, this was a study started quite a few years ago to look at what the durability of agents in patients with relatively newly diagnosed diabetes. And they randomized patients to receive on top of metformin either liraglutide basal insulin, DPP-4 inhibitor sitagliptin, or glimepiride. And their endpoint was to look to time to failure. So, looking at when their A1Cs climbed above 7%. So, this was a group of individuals that had diabetes of relatively short duration, I think they had to be less than four years, and their baseline A1C was in the mid-7s and they were all able to get their A1Cs quickly down below 7. But what they discovered, which I'm not surprised at is that the durability of glycemic control was longer with liraglutide and basal insulin that it was with sitagliptin or glimepiride. Now, what I was a little disappointed in is the duration of the excess durability was measured only in a matter of a few months. It wasn't like we're looking at a year or two years beyond. But I think there's gonna be a lot of information that we can get from these studies looking at people and how much residual insulin they how weight affected it and also the duration of diabetes. So, I'm anxious to see some of the sub-analysis of

the data.

Dr. Anderson:

John, I'm gonna let you weigh in on sessions you thought were informative and interesting.

Dr. Buse:

Yeah. I will comment since I know Carol was gonna focus on a lot of the big clinical trials I also had the opportunity to listen to some of the awards and they gave the Banting Award to Jens Holst who's a long-standing investigator in Copenhagen, Denmark who gave just a fabulous presentation on the history of development of the incretin class and I imagine soon we'll hear from Carol about two of the studies that she participated in that class. But it bridges very nicely to where the field is moving. We've really made a lot of headway with GLP1 receptor agonists. We now have semaglutide at high dose being associated with weight loss. There were a bunch of presentations on the so-called STEP program and a new dose of 2.4 mg of semaglutide marketed for obesity with really spectacular results, 15% loss of body weight, that sort of thing. But now to the next generation of drugs, which is combining agonists from the class, so Dr. Holst just did a wonderful job of presenting those.

The other big award that the American Diabetes Association gives is the so-called Outstanding Scientific Achievement Award. I think you have to be under the age of 50 to get it and a woman Kristen Nadeau from the University of Colorado got it this year. She's a pediatric endocrinologist and she did a just beautiful job reviewing. 15 years of her research in pediatric endocrinology in type 2 diabetes and demonstrated that diabetes in children really is different from type 2 diabetes in adults. It's not just the same diabetes in smaller people. I think those insights are gonna be really important for our treatment of type 2 diabetes, particularly in children moving forward.

Dr. Anderson:

Great. Thanks. So, Carol, other interesting sessions that you attended?

Dr. Wysham:

So, the sessions that John was referring to are a couple studies that I participated in the ones that got probably the biggest buzz were the studies looking at tirzepatide. So, tirzepatide is a dual-agonist, which activates the GIP receptor or the GLP1 receptor and in doing so, likely takes advantage of the activities of both hormones to give even greater A1C reduction and pretty substantial weight loss. Now, we do have two GLP1 agents that have been marketed for obesity where they've taken the doses above those that we have marketed for diabetes and what they've shown is that you can get greater weight loss, but your A1C reduction seems to level off at the doses that they market for diabetes, whereas, this particular agent was associated with A1C reductions that were in the 2 to 2.5% range and these are pretty typical starting points that between 8 and 8.5, like most of the modern studies that we have. So, we have markedly higher A1C reduction than we've seen with other agents and in addition has that same 10 to 15% body weight reduction that we were seeing with the high-dose semaglutide. So, obviously the indication is going to be they're going to go for indication for diabetes, since unfortunately, I don't think Novo was able to get the diabetes indication for the high-dose semaglutide, as of yet.

The typical side effects of this medication or this particular medication were very typical for what we see with GLP1 GI side effects of nausea, dyspepsia, diarrhea low instance of vomiting. It did, in a head-to-head study with semaglutide 1.0 have greater percent of patients with GI side effects. But again, these could be mitigated by starting at a low dose. And unlike the trials, in clinical practice, if somebody bumps up to a dose and can't tolerate it, they can still back off, and believe me, the dose response for the A1C was relatively shallow, I mean it was definitely there, but if you can still get 2.2 or 2.4% reduction in A1C with a middle dose that's gonna be better tolerated, obviously in clinical practice, we're going to be doing that.

Dr. Anderson:

For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Anderson, and today I'm joined by Dr. John Buse and Carol Wysham, hosts of *Diabetes Discourse*, to discuss highlights and key take-aways from this year's ADA Scientific Sessions.

Dr. Anderson:

OK, Carol, any other sessions that you attended that you'd like to talk about?

Dr. Wysham:

Yeah, I think the last one, again, it's in that incretin field has to do with the AMPLITUDE study, and that was looking at a long acting GLP1 receptor agonist, efpeglenatide. It is a exendin-based GLP1 receptor agonist, similar to acinitides. Sanofi was developing this along with another company and started the cardiovascular outcome trial called AMPLITUDE. And they randomized about 4,000 patients and they were pretty typical cardiovascular outcomes study you know 90% of them had cardiovascular disease. And what they were able to show, over a relatively short period of time, it was just a mean follow-up of 1.8 years, there was a 27% lower risk of major adverse cardiovascular events in the patients who are randomized to efpeglenatide compared to placebo. Also, showed a decreased risk for hospitalizations for unstable angina, composite renal outcomes, similar to what we've seen in some of the other GLP1 receptor agonist studies and a 27% lower risk of either MACE or non-cardiovascular death. So, very similar, again, to the outcome studies that we have seen with the other GLP1 receptor agonists; a little sicker population than, than what most of them were. But I think it puts to bed that theory that in order to get cardiovascular benefit, your GLP1 receptor agonist has to come from a base of a human GLP1 in that this extended base molecule also showed that just activating the GLP1 receptor agonist was all that was needed.

Dr. Anderson:

That's pretty surprising result for 4,000, which is a relatively on the smaller side of the GLP1 receptor agonist trials in 1.8 years median observation period, that's pretty impressive data.

And I also wanna remind everyone, one of the most interesting sessions I saw was the Hundredth Celebration of the discovery of insulin. It never gets old to me seeing the dramatic presentation of what changed overnight almost, at the Banting and Best discovery of insulin and how it got quickly crystallized and produced and distributed to a pretty big population in a pretty short period of time. So, I really enjoyed the session. They had some new novel insulin lectures after the historical presentation. But I thought it was really nice to realize that it's a hundred years ago.

Dr. Wysham:

Well, I know John, I'm the oldest of the group, so I can say that advances of insulin in the last thirty-five years have been remarkable, but the other advances in management of cardiovascular risk factors now having SGLT2s for prevention of renal disease, as well as the technology in CGMs and hybrid close-loop insulin pumps, to me those are much more important than what insulin that our patients are able to get.

Dr. Buse:

The magic of a hundred years ago as you went from a disease that was uniformly fatal in weeks to months to a disease now, I saw a patient today who's had type 1 diabetes for sixty-five years, he's 90 years old and living pretty well.

Dr. Wysham:

I don't want to minimize that discovery, but as I read more and more about these new formulations of insulin, I think about the other things that we have available for our patients and you know I become a little less enamored with the fancy new insulins. It's the fancy new technology that's got my interest.

Dr. Buse:

Yeah, but the fancy new insulins are the ones that drive the technology. I mean, at least for these pump-sensor combinations, at least theoretically the faster the insulin, the better it's gonna work.

Dr. Wysham:

Don't you think it's the other way around? It's technology driving the need for the faster insulin as we discovered, you know, more and

more about how sluggish the current insulins are, it is driving the development faster insulins. But I'm not sure that we have made the leap to something that is gonna make a dramatic difference.

Dr. Buse:

Yeah, we'll see. I think we're getting very close. And it is a game of interval change. I mean, twenty years ago we were able to do pretty well with multiple daily injections of human insulin as was used commonly in the DCCT trial, I mean we showed that that makes a big difference. Many of those patients in the intensive arm of the DCCT have done extraordinarily well. I think these changes in the insulin formulations have certainly made a difference. But I agree with you, the CGM the algorithms, type 1 diabetes is looking better and better every day.

And, you know, that brings me to another session that I thought was really extraordinary. On Monday they had the reveal of the management of type 1 diabetes in adults the 2021 Draft ADA/EASD Consensus Report, which was co-chaired by Richard Holt and Anne Peters. So they have this about 70-page document double-spaced, that was discussed and presented, is now up for review and comment from the general public. It's really a remarkable document that covers the whole waterfront of what needs to be done to meet the standard of care in type 1 diabetes management.

Dr. Buse:

It was an extremely well-done presentation. I mean, nothing earth shattering, it's really wonderful to see all the recommendations in the same place. And I think particularly, for primary care doctors that are in rural settings where they don't have the luxury of sending their patients with type 1 diabetes to an endocrinologist, certainly worth a quick review to remind yourself of some of the details in the recommendations.

Dr. Wysham:

That's good to hear. Look forward to seeing it.

Dr. Anderson:

Yeah, and I think for primary care, I think all of the new data surrounding SGLT2 inhibition and heart failure and surrounding renal protection and then having mineralocorticoid receptor antagonist coming along for finally in primary care we have some new tools that should hopefully change the way we think about managing our patients with type 2 diabetes and managing those with CKD and heart failure who don't have diabetes.

Dr. Wysham:

I find myself seeing patients without diabetes for their thyroid and they come out of the hospital with heart failure and I look and say, "How come you're not on an SGLT2 inhibitor?" It's just trying to get that evidence into the clinic is, has been a challenge, I think.

Dr. Anderson:

Yeah and I think it's gonna be a slow trickle rather than a fast rush, unfortunately. There's just so much to digest there, I think from a primary care standpoint.

Dr. Buse:

Well, that was another great session. Carol, you keep reminding me of good stuff that I saw. So, there was a debate between Sandy Doss, a cardiologist from Texas and Jennifer Green, an endocrinologist from Duke, about whether we're there yet with regards to starting an SGLT2 inhibitor or a GLP1 receptor agonist in the inpatient setting in people with fairly advanced chronic kidney disease or with heart failure, or cardiovascular disease. And I have to say, Dr. Doss, the cardiologist did a great job on the pro-argument, pointed out things that I wasn't really aware of. I mean I might've guessed, but it turns out that someone that had an admission for heart failure in the last year has a just dramatic reduction in their risk of re-hospitalization with an SGLT2 inhibitor prescription. If I remember it was the number needed to treat to prevent a hospitalization in that population was just 10.

Dr. Buse:

And Jennifer Green did the prudent thing as the endocrinologists often do and said, "Well, you know, it's all, it's all good to say, yeah, start it in the hospital, but, often when you have someone in the hospital the focus really is getting the people out of the hospital." And to the extent that you might slow down that transition by feeling like if I'm starting a drug in the hospital, I need to make sure that everything is OK. Do I need to reduce the insulin dose, do I need to change the diuretic dose, etc. etc. The way to go is for endocrinologist and cardiologists and primary care doctors to work better together.

Dr. Wysham:

I'm gonna push back a little bit on that because we have examples of, with the statins, way back when, where the cardiologists thought it was the job of the primary care doctors to start the statins for their heart patients and easily 20% or so of patients with known cardiovascular disease and indications for statins were actually started on them, and we were able to increase that to 60% by starting the medication while the patient was either in the hospital or upon discharge. And we know that patients who look at a drug as being something for their heart are going to be more adherent than if they're looking at it for something for their cholesterols, per se. And so, I think the same can be said about these agents. And I think, I agree with you, it has to be a systemic change but we can train educators, nurses, other people in the hospital to do the appropriate education of the patients on how to manage if they don't have diabetes then they don't have to have adjustments of their insulin, obviously. And, you know, if they are patients with diabetes then yeah, you definitely have to make sure you've got the appropriate knowledge base to make the changes. But I still think they should be started at very latest on discharge.

Dr. Buse:

So, they had a debate. I agree with you. It is complicated, though. There's all these prior authorizations, hospitals usually don't deal with. There's a lot of places where you can hold out on the job on the inpatient side trying to pull this off. So, the debate was really interesting. I agree with you, Carol, in an ideal world, we would start it in the hospital, but we live in a far-from-ideal world.

Dr. Anderson:

Well, I think the key is ideally you get it started at discharge but you're right, John, I mean, all the prior authorizations, the hoops you have to jump through, they're not gonna have the same samples I have in the outpatient setting. But I think it really begs the question of this hand-off, inpatient to outpatient has to be done with some precision and some talk between providers, instead of, "Here's a discharge summary from the hospital."

Dr. Buse:

One other thing I'll add is though in this instance, Dr. Doss, the cardiologist made this compelling argument for how this really needs to be done and blah, blah, blah, blah, blah, you know, the truth of the matter is cardiologists are not doing a great job of starting these drugs in the outpatient setting or in the inpatient setting. And there is a level of discomfort which he addressed that, if I start this drug and the patient has problems with hypoglycemia, what am I gonna do? If I start this drug and there's gonna be changes in their diuretic dose, I don't have the bandwidth to see people back quickly, etc. etc. etc. He did a good job of debunking most of those kinds of arguments. But it is a bit of an uncharted territory for the cardiology community and for some primary care doctors, as well.

Dr. Anderson:

Well, that's all the time we have for today, but I wanna thank my two fellow hosts for joining me to discuss this year's ADA Scientific Sessions. Dr. Buse, Dr. Wysham, it was great speaking with you both, today.

Dr. Buse:

Thank you.

Dr. Wysham:  
Thank you.

Dr. Anderson:  
I'm Dr. John Anderson. To access this episode and others in our series, visit [ReachMD.com/DiabetesDiscourse](https://ReachMD.com/DiabetesDiscourse), where you can Be Part of the Knowledge. Thanks for listening.