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Key Insights from GRADE: Exploring Data on Glycemia Reduction in T2D

Dr. Buse:
Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And joining me to share insights on glycemia reduction for patients with type 2 diabetes is Dr. Deborah Wexler. Dr. Wexler is an Associate Professor of Medicine at Harvard Medical School and Associate Clinical Chief of the Mass General Hospital Diabetes Unit and Clinical Director of the Mass General Hospital Diabetes Center.

Dr. Wexler, thanks for speaking with me today.

Dr. Wexler:
Thanks for having me. I'm delighted to be chatting with you.

Dr. Buse:
So, we're talking about the GRADE study, which was published recently in The New England Journal of Medicine. Can you provide the background for why the GRADE study was conducted?

Dr. Wexler:
I can. I should say that you and I were both GRADE investigators, and looking forward to discussing it with you. So, when GRADE was designed in 2012, we had a set of diabetes guidelines that recommended that patients with type 2 diabetes be treated with lifestyle measures and metformin, but the ACP and many other organizations have released several evidence reviews showing that there was really no evidence to guide which second glucose-lowering medication should be added to metformin in type 2 diabetes, and GRADE was really designed to fill that evidence gap. It was a comparative effectiveness trial comparing the four most commonly used classes of diabetes medications in use at that time.

Dr. Buse:
Great. And the classes were a sulfonylurea, insulin DPP-4 inhibitor, and a GLP-1 receptor agonist. Why was the SGLT2 inhibitor, or a thiazolidinedione, not included in the trial?

Dr. Wexler:
Well, it's a good question. And the reasons are different for each. So, at the time that the trial was designed in 2012, and of course, it was launched in 2013, the use of thiazolidinediones, such as pioglitazone, was on the wane in the wake of earlier evidence suggesting that there were concerns about their use. We now know they have some utility, but they were really not in widespread use at the time. In terms of SGLT2 inhibitors, they actually had not been approved at the time that GRADE was designed and launched. GRADE was actually specifically designed to be a very long-term trial because the vast majority of trials in the management of hyperglycemia in type 2 diabetes are, of course, placebo-controlled and relatively short-term trials designed sort of for purposes of registration. Yet we know that people with type 2 diabetes take medications over many years, and the goal was to really perform a head-to-head comparison over many years to accurately represent the way people with diabetes take and use these medications in real life.

Dr. Buse:
Wonderful. So, with that as background, what were the key design features of the trial?

Dr. Wexler:
Well, GRADE was pretty unusual in that it was a four-arm randomization, so that's not very common. It was a head-to-head comparison of the four medication classes. Patients had type 2 diabetes were treated with metformin with hemoglobin A1c 6.8 to 8.5 at baseline. That A1c window was designed to capture people who would have a chance of success with each of the medication classes being

tested in the trial. Patients had a run-in period in which the metformin was optimized and then they were randomly assigned to one of the four medications. The second assigned medication was then continued until the A1c reached 7 percent or greater. If the A1c did hit 7 percent or greater, we observed patients for another three months until their next quarterly visit to make sure that that result was confirmed because, as we know, people with diabetes can have A1cs that bounce around a bit. Once that A1c was confirmed, we called that the primary outcome. We then observed people on the randomly assigned combination until the A1c hit 7.5 percent, and at that point, all patients had glargine added if they weren't already taking insulin glargine, and for the glargine arm, prandial as part was started at that time point.

Dr. Buse:
Great. So, what were the results?

Dr. Wexler:
Well, I think before I give you the topline results, I want to just highlight a couple of important features of GRADE. There were over 5,000 patients from around the United States enrolled in GRADE, and they were representative of a primary care metformin-treated population. Mean age was about 57. And, importantly, this was a very diverse cohort.

People were then followed for five years, and we were able to observe a number of things, not just the topline findings but kind of how people did in the trial. So, for example, we were able to observe adherence in a setting in which people were provided with medications, and what we observed is that people really did adhere to their randomly assigned second medication with most people staying on it but actually higher discontinuation rates in the glimepiride and liraglutide arms of 23 percent compared to about one in five discontinuing sitagliptin but only 14 percent discontinuing insulin glargine. So that in and of itself I think was an interesting finding. But then we really get to the, you know, big sort of glycemic findings of GRADE, and what we observed is that actually, the majority of participants in GRADE progressed to the primary outcome of A1c of 7 percent or higher within the first two and a half years of the trial.

Now, this is what we have observed in prior trials. This was seen in the UKPDS. This was seen in ADOPT. I think there might have been some hope that with newer agents we might have seen a different pattern, but in fact, the pattern was similar, showing that type 2 diabetes remains a progressive condition. That said, over time with protocol management, by the end of the trial at five years, people did have A1cs close to target at baseline.

In terms of the comparison among the four treatment arms, we observed that the injectable therapies, glargine, and liraglutide, maintained glycemic control more effectively than the sulfonylurea glimepiride, and glimepiride in turn was more effective than sitagliptin, so we really were sort of able to see a difference there, and that difference was particularly notable in people with higher A1cs in whom sitagliptin was less effective.

So those were sort of the topline glycemic results, but there were also a bunch of subtle nuanced findings that I think really are informative for people who manage diabetes every day.

Dr. Buse:
For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and today I'm speaking with Dr. Deborah Wexler about glucose-lowering medications in type 2 diabetes.

So, with that teaser, what do you think the key implications are for clinical care?

Dr. Wexler:
For those who are just joining in, the injectable therapies, glargine insulin and liraglutide, were more effective than glimepiride, which was more effective than sitagliptin, but there were a number of nuanced findings. First of all, severe hypoglycemia was actually very uncommon, but surprisingly, it occurred more often in the glimepiride group at a rate about 2 percent than the other groups. I think when we think about glucose-lowering medications, we often worry about hypoglycemia and insulin, but in fact, it was more commonly seen with sulfonylurea.

The other kind of surprising findings were weight. So, on average in this trial, liraglutide was associated with the most weight loss, as you might expect. Sitagliptin had on average the second most weight loss, but both glargine and glimepiride were on average weight neutral by the end of the trial. People tended to actually lose a slight amount of weight, over the five-year period of follow-up. Now, again, this little bit is counter to conventional wisdom. We often think of these medications as causing weight gain, and indeed they did cause weight gain. The adverse outcome of weight gain of 10 percent or greater was more common in the glargine and glimepiride arms. Participants taking those medications who had weight gain of 10 percent or greater than had the medications stopped. But when you stopped it in those people, on average the people who remained on glargine and glimepiride, which was the, you know, majority of the rest of the patients, really did very well on those medications over time. So in terms of my own thinking in glucose-lowering therapy, I think that all of these medications actually can be used safely and well, and we've learned a little bit more about how that can be done.

Dr. Buse:
I wonder if you want to tell us about your next big thing. I mean you have been one of the people that sort of evaluates diabetes treatments and what's the optimal therapy in large groups of patients. What do you think the next big question is? And how are you trying to address it?

Dr. Wexler:
Thanks for asking. I think what we learned from GRADE is the value of comparative effectiveness research. We so often see placebo-controlled trials, but in real life, we don't offer patients a medication or placebo. We really need to do head-to-head comparisons. And I think the head-to-head comparison that we all would like to understand a little better is with the newer medications: SGLT2 inhibitors and GLP-1 receptor agonists. Here we have these very effective therapies not only for glucose lowering and weight but particularly for cardiovascular heart failure and kidney progression outcomes. We, I think, do need to understand more about how those perform in a head-to-head comparison and how well they work together.

Dr. Buse:
Yeah. When you get an answer, we'll definitely have you back on ReachMD. I'm dying to know that answer too.

Dr. Wexler:
Thank you.

Dr. Buse:
Before we close today, any final thoughts you'd like to share with the audience?

Dr. Wexler:
You know, I think there were a lot of take-home findings from GRADE, but as someone who takes care of people with diabetes every day, I learned a lot from taking care of participants in GRADE and from the results in GRADE. It has helped me to use sulfonylureas more safely, and it has helped me to consider early insulin use. We don't usually think about insulin as the next-step therapy after metformin, but in fact, participants who were treated with insulin had very good outcomes, it was safe and effective, very few side effects, and did extremely well. And so, you know, I think exploring patient preferences and goals is super important and remains important for choosing glucose-lowering therapy, and GRADE will help us decide in the absence of comorbidities that really dictate which medication to choose. We really now have a way of saying the pros and cons of each medication with much more data and accuracy than we did in the past.

Dr. Buse:
Yeah, I agree completely. I think the one other thing was we allowed patients up to an A1c of 8.5 percent, and I do think the performance of the DPP-4 inhibitor class, you know, here we use sitagliptin, was pretty disappointing. And it does kind of highlight that if you're aiming for an A1c target of less than 7 percent, you really probably need to limit your use of DPP-4 inhibitors in people that have A1cs, you know, much higher than the mid to high 7s, at least if you want to get to that target and stay there for more than a few weeks or months.

Dr. Wexler:
Thank you for the opportunity to come on to this podcast and discuss the results of GRADE. I would encourage everyone to go to the papers. There's a pair of papers in The New England Journal from earlier this year.

Dr. Buse:
Well, thank you. With those final thoughts in mind, I'd like to thank my guest, Dr. Deborah Wexler, for sharing her research on glycemia reduction in patients with type 2 diabetes.

Dr. Wexler, it was great speaking with you today.

Dr. Wexler:
Great to be here. Thank you for having me. Thank you for the opportunity to come on to this podcast and discuss the results of GRADE. I would encourage everyone to go to the papers. There's a pair of papers in The New England Journal from earlier this year.

Dr. Buse:
For ReachMD, I'm Dr. John Buse. To access this episode and others from our series, visit ReachMD.com/DiabetesDiscourse where you can be Part of the Knowledge. Thanks for listening.