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Explore Impacts Of Glucose-Lowering Medications in Addition to Metformin

Dr. Buse:

For patients with type 2 diabetes, treatment with glucose-lowering medications in addition to metformin can be an effective approach, but do we understand the full effect this therapeutic combination can have on microvascular and cardiovascular complications in diabetes?

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And joining us to share highlights from her research on the glycemia reduction in type 2 diabetes study is Dr. Jennifer Green, who is a Professor of Medicine at Duke University.

Jennifer, thanks for being here today.

Dr. Green:

It's my pleasure.

Dr. Buse:

We previously had the opportunity to discuss the GRADE study with Dr. Deborah Wexler, and she reviewed the glycemic outcomes that was published as a companion paper with your paper in *The New England Journal*, and your paper focuses on cardiovascular and microvascular outcomes. But for those that are unfamiliar, can you give us a brief overview of the GRADE study and its outcomes?

Dr. Green:

Of course. So, GRADE was a long-term comparative effectiveness study that enrolled just over 5,000 people with type 2 diabetes who were on the maximum tolerated dose of metformin and really needed to have a second drug added to achieve adequate glycemic control. So, once they were enrolled in the study, they were randomized to one of four treatments including the DPP-4 inhibitor sitagliptin, the sulfonylurea glimepiride, the GLP-1 receptor agonist liraglutide, or once-daily basal insulin glargine. And really, the intent of the trial was to determine how effective each of those interventions was in both achieving and maintaining good glycemic control essentially defined by a hemoglobin A1c of less than 7 percent.

Dr. Buse:

Perfect. And though that's not the focus of your paper, could you just give us the topline result regarding the primary glycemic outcome of that four-arm randomization?

Dr. Green:

Of course. And even though we're going to talk about complications in a minute, it's really important to remember that this was a study focused on glucose control and glycemic outcome, so the rest of the information is secondary, but the focus was really on glucose control. Now, what we found at the end of the day after a mean five years of follow-up of that just over 5,000 patients was that two of the interventions, so the insulin glargine therapy and the liraglutide therapy, were most effective in keeping patients' glycemic control within the target range. Less likely to be successful were the glimepiride and sitagliptin treatments. Approximately a third of people failed from a glycemic perspective the addition of insulin or liraglutide to metformin. The higher percentages than that failed to achieve and maintain adequate glycemic control in the other two arms. I would note though that very large percentages from my perspective in all of the treatment arms failed to maintain good glycemic control on two medicines over the entirety of the five years, so clearly, we still need to learn more.

Dr. Buse:

Wonderful. So let's start talking about the focus of your work, so microvascular complications and cardiovascular complications. Why

don't you tell us about the microvascular results from the trial?

Dr. Green:

Sure. Sure. So, I mean, to make a long story short, when we compared the rates of various microvascular complications between these four different groups assigned to the four different glucose-lowering medications, it really wasn't evident that there was a significant difference in the risk of these microvascular outcomes that was attributable to the particular second medication that was added, so the good news is they all appeared to be equally effective from that perspective.

Dr. Buse:

And you're doing a great job of making things simple that were really pretty complex in the trial and in the reporting.

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. Jennifer Green about microvascular and macrovascular outcomes from glucose-lowering medications.

So let's switch gears now and look at the cardiovascular outcomes. How did glucose-lowering medications in GRADE play a role there?

Dr. Green:

Yeah, that's a really important question. And, and although, again, this was not a trial that was designed or necessarily originally powered to assess the impact of the different therapies on cardiovascular outcomes, there was a prespecified analysis looking at exactly just that at the end of the trial, and interestingly, what we found was that the individuals assigned to liraglutide therapy appeared to have a lower risk of a wide variety of cardiovascular events assessed together as a composite endpoint over the course of the study than was seen in the other groups and, in particular, compared to those who were treated with sitagliptin, insulin glargine or the glimepiride, just to refresh everyone's memory. So, although it was difficult, in our analyses to draw firm conclusions about the impact of liraglutide therapy on cardiovascular outcomes compared to the other interventions, it's certainly thought-provoking and something that warrants further study.

What's really interesting that for the most part, the people enrolled in GRADE did not have established cardiovascular disease. If I remember correctly, only around 6, 6.5 percent of people enrolled in the study had had a prior myocardial infarction or cerebrovascular accident, so this was a relatively low risk group of people for subsequent cardiovascular events. And it is really interesting and potentially very important to have found a difference in outcomes with GLP-1 receptor agonist therapy in this lower-risk group. So it's very intriguing and I think warrants additional study.

Dr. Buse:

Thank you. And how do you think this paper will impact treatment in general for people with type 2 diabetes? Or perhaps more specifically, has it changed the way that you practice?

Dr. Green:

That is an interesting question. Well, I hope that it will change practice in several different ways, one of which is that it is evident from the trial results that there are certain interventions used as second-line drug therapy for glucose lowering that are more effective, and, and I think it's important for us to understand that when we're recommending particular medical therapies to our patients with type 2 diabetes. And I think the more mileage that we can get out of a given drug the better and I always try where possible to simplify diabetes medication regimens and reduce medication and injection burdens where possible. So I think it's helpful in that respect, but I also think we need to be cognizant of the fact that very large percentages, from my perspective, of people couldn't be controlled adequately over five years with two drugs. So we'll also need to really think about that and make sure that we're not waiting too long to appropriately intensify therapies and exposing patients to a higher risk of complications due to uncontrolled hyperglycemia. So those are at least a couple of reasons to do that.

You know, all of the interventions had similar outcomes from the microvascular perspective, so I think the take-home message for me is please do something. Add a drug if needed to reduce the risk of microvascular complications. Doing something is clearly better than nothing. And again, from the cardiovascular outcomes perspective, I don't think that we can conclusively say right now that treatment with liraglutide compared to these other agents will clearly reduce the risk of cardiovascular complications in these lower-risk patients, but it may be true. It may be true. I would love to see additional data, additional studies support that hypothesis.

Dr. Buse:

That is so well said. Thank you for that, Jennifer. Any final thoughts that you have for the audience before we close up?

Dr. Green:

I feel like I've talked a lot already, but again, I think the take-home message or final thoughts from me would be not to wait when it comes to diabetes management. We may need to think about treating people with type 2 diabetes with more than one glucose-lowering

medication at a very early stage so that perhaps we can change this trajectory and likelihood that large percentages of people will have inadequate glycemic control year after year, so that would be my suggestion. Again, not something that we specifically tested in the GRADE study, but I'd love to do better than was seen in this clinical trial where patients were clearly provided with all of their diabetes medications and had a lot of hands-on support. I think the GRADE study results clearly indicate a need to do more and learn more about type 2 diabetes management.

Dr. Buse:

Again, very well said. That's a great note for us to end on. And I'll just add that usually, I add more to the conversation, but you said everything so well, I really feel like I didn't have much to do here, so thank you for that.

Dr. Green:

Thank you. It was a pleasure to be here.

Dr. Buse:

So we'd all like to thank Dr. Jennifer Green for sharing about microvascular and cardiovascular outcomes from the GRADE study in patients with type 2 diabetes. Jennifer, it was a pleasure speaking with you today.

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.