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VOLUME 2 — ISSUE 1: TRANSCRIPT, DR. ANDREW AHMANN

DR. KATHLEEN DUNGAN: I'm Dr. Kathleen Dungan, *e*Diabetes Review program director. I'm speaking with Dr. Andrew Ahmann from the Oregon Health and Science University in Portland, Oregon and one of the authors of the FLAT-SUGAR study. Dr. Ahmann, thank you for joining me today.

DR. ANDREW AHMANN: Kathleen, it's my pleasure to talk with you this morning.

DR. DUNGAN: FLAT-SUGAR investigated the effect of the GLP-1 agonist exenatide versus prandial insulin on glycemic variability in patients with type 2 diabetes at high cardiovascular risk. Can you give us a brief summary of these findings?

DR. AHMANN: This was basically a pilot study, a proof of concept study to guide future studies. What it showed was that exenatide's capacity to control glucose when added to basal insulin was equivalent to that seen with meal doses of rapid-acting analog insulin added to the basal insulin, at least within the target range we used for the study. In the process, the primary outcome measure of glucose variability, which was defined by coefficient variation, was statistically improved in the exenatide group compared to the bolus insulin group.

Another measure of variability, mean amplitude of glycemic exertion, was also statistically different, and several other secondary outcome measures of variability trended in that same direction. There was also a trend toward less hypoglycemia, but this was actually not statistically significant in this relatively small pilot trial.

DR. DUNGAN: With respect to glycemic variability, why is it important compared to what we're used to, which is the A1C and maybe mean glucose?

DR. AHMANN: We generated the hypothesis because there's been some question about whether there are independent effects of variability in diabetes complications. This comes from several studies that would suggest that variability and postprandial excursions, for example, contribute to oxidative stress and other metabolic consequences that then lead to diabetes complications. However, to advance the study of this hypothesis, the first thing we need to prove is that there's an intervention that appreciably decreases variability, which was really the primary intention of this study.

DR. DUNGAN: That's actually pretty hard to do, because you're dealing with medications that lower both mean glucose and variability. What do these results add to our understanding of cardiovascular risk and cardiovascular events in type 2 diabetes?

DR. AHMANN: With regard to the outcomes of this particular trial, I don't think that the results really give specific information on cardiovascular risk. There was an initial look at rhythm disturbances, but it showed no obvious differences between the two methods of treatment. The analysis of abundant Holter data, however, has not yet been completed, and it's actually a fairly tedious process to look at all the changes that may relate to ischemia or other interval changes and so forth.

The study was certainly not powered as well to look at other cardiac events such as coronary artery disease events. The hope is that a bigger study would come

from this that would provide a more definitive result with respect to cardiovascular effects.

DR. DUNGAN: I agree, that would be exciting. Do you think glycemic stabilization in this case is related to the specific GLP-1 agonist that was used? Could it be a class effect?

DR. AHMANN: There's some evidence that short-acting GLP-1 agonists have a more profound and specific effect on postprandial glucose excursions than we see in the long-acting GLP-1 agonists, where there's some benefit on postprandial glucose and also some effect on fasting glucose. However, there's been no direct comparison of the overall glucose variability with these agents of different duration.

In this study, as in some other studies, there was evidence that the exenatide did not control the post-lunch glucose excursions well. This leads to the question of whether three times a day exenatide or longer acting GLP-1 agonists would have advantages. At this point, there's been no such comparison, so we really don't know.

DR. DUNGAN: I see. Well, Dr. Andrew Ahmann from the Oregon Health and Science University in Portland, thank you for sharing your thoughts on FLAT-SUGAR.

DR. AHMANN: My pleasure.