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VOLUME 2 — ISSUE 1: TRANSCRIPT, DR. JENNIFER GREEN

DR. KATHLEEN DUNGAN: Hello, Dr. Kathleen Dungan, *e*Diabetes Review program director. I'm on the phone with Dr. Jennifer Green from Duke University and the Duke Clinical Research Institute. She is one of the authors of the TECOS study. Dr. Green, thank you for joining me today.

DR. JENNIFER GREEN: It's my pleasure.

DR. DUNGAN: TECOS investigated the effect of the DPP-4 inhibitor sitagliptin on cardiovascular outcomes in type 2 diabetes. Can you give us a brief summary of the findings?

DR. GREEN: Certainly. The trial was designed specifically to address the cardiovascular impact of diabetes care that either included or did not include the medication sitagliptin. Patients were randomized to that medication or a matched placebo and followed for approximately three years on average. We found that sitagliptin therapy did not increase or significantly decrease the risk of a composite cardiovascular endpoint, which included cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina.

DR. DUNGAN: Can you tell us how these results compared to some of the other recent cardiovascular outcome studies of DPP-4 inhibitors? I'm thinking specifically of the EXAMINE trial with alogliptin and the SAVOR-TIMI saxagliptin trial.

DR. GREEN: Those trials were similar in the sense that they were designed to also assess the cardiovascular safety of diabetes care, including those DPP-4 inhibitors. All of the trials very convincingly showed that the DPP-4 inhibitors under study as a component of diabetes care did not adversely impact rates of cardiovascular complications, including primarily cardiovascular death, myocardial infarction, or stroke.

However, there were some differences with respect to heart failure outcomes among these studies. In the SAVOR-TIMI 53 trial, which studied the effect of saxagliptin therapy in type 2 diabetes, they did find a significant increase in rates of hospitalization for heart failure in patients assigned to saxagliptin therapy as compared to placebo. In the EXAMINE trial, there were greater numbers of alogliptin treated patients hospitalized for heart failure compared to those treated with placebo, although the difference was not statistically significant. But in TECOS there was absolutely no difference in rates of hospitalization for heart failure in our two treatment groups.

DR. DUNGAN: Where do we go from here? Is it possible that there could be a class effect? Or, in this case, it would have to be limited to one specific drug. Do you think that's possible?

DR. GREEN: That's the million dollar question, and I think it's most accurate for me to say with confidence that there does not appear to be an increased risk of hospitalization for heart failure with sitagliptin. In turn, I think it's difficult to say that there is a class effect associated with these various medications.

Now, whether the findings of the SAVOR-TIMI study indicate that saxagliptin poses a significant increase in risk for hospitalization for heart failure is still a matter of some debate. It may be that there are major physiologic differences between the various DPP-4 inhibitors, or as some think, the statistical outcomes may represent chance.

What's difficult to reconcile with the findings is the absence of a good physiologic explanation for why DPP-4 medications might increase risk of heart failure; however, these medications may have effects that have not been well studied and should be scrutinized more carefully in the future.

DR. DUNGAN: I see. One last question. Can you comment on the glucose lowering effects, it seemed as though the A1C lowering was a bit modest.

DR. GREEN: Particularly in the TECOS trial, that was completely intentional because we wanted to study the cardiovascular effect of these drugs as separately as possible from their glucose-lowering effect. So, for example, if the sitagliptin-treated group had had much tighter glycemic control than did the placebo-treated group, it might've confounded our interpretation of the results. For example, a better degree of glycemic control over time might in turn have reduced the risk of cardiovascular complications and introduced a confounding factor in our ability to interpret purely the cardiovascular effect of treatment with sitagliptin.

DR. DUNGAN: Dr. Green, from Duke University, thank you so much for sharing your thoughts on TECOS study.

DR. GREEN: Thank you for having me.