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Diving into Diabetes: Investigating SGLT2 Inhibitors & Diabetic Ketoacidosis

Dr. Buse:
Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and joining me to discuss his research focusing on SGLT2 inhibitors and the risk for diabetic ketoacidosis is Dr. Antonios Douros, Assistant Professor in the Department of Medicine at McGill University and research investigator at Lady Davis Institute in Montreal, Quebec. Dr. Douros, welcome to the program.

Dr. Douros:
Thank you very much for the invitation and I'm very glad to be with you today.

Dr. Buse:
Outstanding. So let's just dive right in, Dr. Douros. Can you tell us the top-line results of your study?

Dr. Douros:
First of all, I would like to mention that this study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES), which was created in 2011 and comprises a large network of over 100 scientists and other researchers. And its goal is to study the effectiveness and safety of drugs for Canadians. So to this end, we have access to electronic healthcare databases in several Canadian provinces, and also in the United Kingdom, and we are funded by the Canadian Institutes of Health Research. So our study included over 350,000 patients with Type 2 diabetes, from 2013 to 2018. We also conducted molecule-specific analysis. the molecule hazard ratios were 1.86 for dapagliflozin, 2.52 for empagliflozin, and the highest was 3.58 for canagliflozin. These are the main results of the study.

Dr. Buse:
Outstanding. So there have been other reports about diabetic ketoacidosis with SGLT2 inhibitors. How does your data fit into that other literature?

Dr. Douros:
That's a very good question. So we had several case reports from the very beginning that were like safety signals from pharmacovigilance analysis. There were also safety warnings by the FDA and Health Canada and other regulatory agencies. And there were also signals in the landmark randomized trials assessing the efficacy of SGLT2 inhibitors. There was a signal that linked them to DKA; however there was a strong variation in the magnitude of the potential effect, so to give you an idea, the hazard ratios in the RCTs ranged from 1.99 to 10.8. And the results were also rather imprecise given the relatively small sample size that RCTs have. So these were the RCTs. We also had several observational studies that addressed this study question before the CNODES study, but some of the studies have several methodological limitations, so interpreting the results was a little complicated, and some other studies had, for example, rather younger patients with a mean age of like in their 50's, which is not necessarily representative of their real-world practice. But most of the observational studies also showed an increased risk of DKA with SGLT2 inhibitors.

Dr. Buse:
I was most taken by the idea that the point estimate of the hazard ratio was 3, but the confidence interval's pretty narrow – from basically 2 to 4. So that's outstanding. You know, there's a difference in our understanding of hazard ratios or risk ratios, versus the absolute risk. Could you tell us about the absolute risk for DKA in this population?

Dr. Douros:
So, as you said, the hazard ratio, or the rate ratio, these are like measures of relative risk, and our results show that there is an almost

threefold increase in the relative risk. However, the absolute risk this is where the rate difference, for example, comes to play – was 1.2 per thousand persons per year. So by using SGLT2 inhibitors, you would have let's say an extra case of DKA per thousand persons per year. So the increase in the absolute risk at the level of the individual patient was relatively low. That being said, with Type 2 diabetes having a prevalence of approximately 10% in North America, and with SGLT2 inhibitors being increasingly used in the treatment of Type 2 diabetes and also other diseases, the risk of DKA at the population level is non-negligible.

Dr. Buse:
Very good. For those of you just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and I'm speaking with Dr. Antonios Douros about SGLT2 inhibitors and the risk for diabetic ketoacidosis. It occurs to me that you have this fabulous network across Canada and including the U.K. It's an outstanding resource to do these kinds of drug safety analyses. Have you looked into anything else with regards to the SGLT2 inhibitors?

Dr. Douros:
Yes, so the study that we're discussing today, where we assessed the risk of DKA, was part of a much larger program that assessed the effectiveness and safety of SGLT2 inhibitors in routine clinical practice. The first study of that program assessed the effectiveness of SGLT2 inhibitors in routine clinical practice. The study was published in the British Medical Journal last year, and we found strong reductions in the risk of cardiovascular morbidity and mortality with SGLT2 inhibitors, compared with DPP-4 inhibitors. And there were two other studies that assessed safety questions. So, the first study assessed the risk of below-knee amputation with SGLT2 inhibitors. As you may know, there was a signal in the CANVAS program, with canagliflozin, there might be an increased risk. Our results were reassuring in this regard. We found no increase in the risk of below-knee lower limb amputation, and also reassuring results were provided by the very last study of that program, where we assessed the risk of urosepsis with SGLT2 inhibitors. That was another potential safety signal, and again, also there, we did not find an increased risk.

Dr. Buse:
Fantastic. Before we wrap up, Dr. Douros, are there any final thoughts you'd like to leave our audience with?

Dr. Douros:
I would like to thank you again for the interest in our study and for the invitation, and I would like to mention and to highlight the importance of drug safety studies, after market approval, because these studies help us improve our understanding of the safety profile of medications in routine clinical practice.

Dr. Buse:
Well, with those takeaways in mind, I want to thank my guest, Dr. Antonios Douros, for joining me to discuss SGLT2 inhibitors and the risk for diabetic ketoacidosis. Dr. Douros, it was great having you on the program.

Dr. Douros:
Thank you very much.

Dr. Buse:
I'm Dr. John Buse. To access this and other episodes in our series, visit reachmd.com/diabetesdiscourse, where you can Be Part of the Knowledge. Thanks for listening.