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Hypoglycemia & the Cardiovascular System: An Inside Look at Emerging Clinical Trial Data

Dr. Anderson:
You're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Anderson and on this program, we're going to hear from Dr. Simon Heller, a Professor of Clinical Diabetes at the University of Sheffield, and honorary consultant physician with the NHS Foundation Trust in the United Kingdom. Here's Dr. Heller now talking about severe hypoglycemia and cardiovascular risk in patients with both type 1 and type 2 diabetes.

Dr. Heller:
We've known for probably around thirty years that a very rare complication of type 1 diabetes can be sudden death. It is incredibly rare, and it became an issue in the late 80s, early 90s when human insulin was introduced actually, by genetic engineering. I was working as a fellow in the U.K. at the time, and my boss, the senior doctor that I worked with had to do a survey in the U.K. because, at an inquest to a young person who died, there was a suggestion that one of them had died because they were on human insulin due to hypoglycemia. So, they did this big survey and a paper was published in *Diabetic Medicine*, and they found that there were rare cases of young people with type 1 diabetes who had been found dead in an undisturbed bed, in the morning. Their partner would go off to work and they'd come home to find them still in bed and they had died almost certainly overnight. And since then, a number of epidemiological studies have been done, ending with a study from Pittsburgh. There's a cohort in Pittsburgh, and they worked out from this study that the risk of sudden death overnight in people with type 1 diabetes, young adults, generally, and teenagers, is probably around ten-fold that of the normal population because we know that sadly some people can die suddenly. And it's been thought to be hypoglycemia, it's circumstantial, and it remains a very rare but obviously tragic condition. We've been doing a lot of research here in Sheffield and we've found changes in heart intervals during hyperglycemia, and we've wondered whether that might be the case and others have done the same.

There's a very famous study which finished in the last 1990s called the UKPDS, it was a study in type 2 diabetes, it was like the DCCT, which was conducted in North America which proved that tight glucose levels could prevent complications. This was a similar study which was conducted in the United Kingdom actually over ten years and they proved that that was the case. And there was a hint that if they kept the glucose going, at a low level for longer, they might've shown benefit in cardiovascular disease, and therefore, three large trials, were conducted, ADVANCE, VADT, and ACCORD, to test that hypothesis. And they ran, during the 2000s, and during those times, I was participating in one, it was called ADVANCE, and there was another one called ACCORD, which, was conducted again in the U.S. And the reason that that was such an important study is that the glucose levels were kept very, very tight, indeed. And importantly, that study was stopped after three years instead of five years because there was an increased risk of mortality, and it was a great surprise because the theory was that mortality would be reduced, but it was increased. The ADVANCE trial, which went on for the full five years, which I was involved in, didn't show any difference. And so there was this question, why would very tight glucose levels increase mortality? There was no proof that it was hypoglycemia or that hypoglycemia was much more common in those treated intensively, the trial was comparing people treated intensively with, sort of, standard therapy. And since then, there's been a whole host of research, some of which we participated in to try and answer the question, how could it be that hypoglycemia could actually increase mortality rather than reduce it and reduce the risk of heart attacks and strokes, which would be the expected benefit of keeping glucose close to normal. And I think the research has shown that there are a number of reasons why hypoglycemia could have bad effects on the cardiovascular system. Because when you are hypoglycemia, you can have a surge of epinephrine, adrenaline, as we call it in the U.K. and that in itself can have adverse effects on the cardiovascular system. It can increase the rate of the heart, it can actually make

platelets more sticky and it can increase inflammation. And all these can have an adverse effect on the heart and cardiovascular system and increase the risk, subsequently of myocardial infarction, or stroke. And so we now have that evidence that hypoglycemia can be harmful and indeed those effects might last for a few days.

Dr. Anderson:
That was Professor Simon Heller talking about severe hypoglycemia and cardiovascular risk in adults with type 1 and type 2 diabetes. For ReachMD, I'm Dr. John Anderson. To revisit any part of this discussion and to access other episodes in this series, visit ReachMD.com/Diabetes-Discourse, where you can Be Part of the Knowledge. Thanks for listening.