RESPONSE TO COMMENT ON FAHRMANN ET AL.

Modification of the Association Between Severe Hypoglycemia and Ischemic Heart Disease by Surrogates of Vascular Damage Severity in Type 1 Diabetes During ~30 Years of Follow-up in the DCCT/EDIC Study. Diabetes Care 2021;44;2132–2139

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We thank Dr. González-Clemente et al. (1) for their comments on our article (2). We showed that in the young cohort with type 1 diabetes (T1D) of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study without baseline macrovascular complications, the adverse effect of severe hypoglycemia (SH) history on the cardiovascular system increased with increasing microvascular severity. We have not investigated whether a dose-response relationship exists because of differences in severe hypoglycemia ascertainment in the combined DCCT/EDIC period (2,3). Our results demonstrate that the association between SH and ischemic heart disease (IHD) is of a complicated nature. We showed evidence that this association is multifactorial.

In exploratory analyses, we investigated cardiovascular risk factors that might contribute to an increased IHD risk in patients with T1D and with SH during ~30 years of follow-up. Our analyses were mainly performed to investigate whether results are consistent with our main analysis. Of 955 patients, 110 experienced a cardiovascular event. The list of potential cardiovascular risk factors was based on the literature (3,4) and available data. It included insulin dose, a clinical marker of insulin resistance (IR) (5), as well as systolic blood pressure, BMI, dyslipidemia, and HbA1c as clinical IR manifestations (5). Estimated glucose disposal rate (eGDR), a surrogate of IR based on waist-to-hip ratio/waist circumference, HbA1c, and hypertension (1,3,5), was not investigated because DCCT baseline data on waist circumference/waist-to-hip ratio or eGDR were not available (3). Time-dependent mean insulin dose, time-dependent current triglycerides, and time-dependent current LDL (but not time-dependent mean and current BMI or time-dependent mean and current HbA1c) were independent IHD factors for individuals with SH. Time-dependent mean systolic blood pressure and baseline microvascular damage severity surrogates were the most important IHD risk factors for this subpopulation, with the latter finding strengthening the validity of our main results. The significance of insulin dose suggests that IR plays a role in pathogenesis of IHD in patients with T1D and with SH. Whether the finding of the statistically nonsignificant HbA1c effect holds true in the future needs to be investigated.

The authors stated that after ~10 years of follow-up in the observational Pittsburgh Epidemiology of Diabetes Complications (EDC) study, IR was an independent coronary artery disease predictor. We would like to point out that in subsequent EDC analyses, eGDR was not listed as a cardiovascular risk factor (4,5). Although HbA1c was not an independent cardiovascular predictor after 10 years of follow-up in the EDC study, it was an independent factor after ~25 years of follow-up (4). Results of analyses become more reliable with longer follow-up times and more events, and the importance of factors might change over time (3,4). In this respect, it is noteworthy that in the authors’ mentioned observational Italian study, 49 of 736 experienced a major cardiovascular event, and in their own study, 10 of 84 were diagnosed with silent myocardial ischemia. These event numbers are small; consequently, these studies need to be cautiously interpreted.

We agree with the authors that IR should be considered a potential IHD risk factor. However, future studies are needed to find a consensus on what IR surrogate is practical and most efficient in clinical practice. At the same time, more controlled trials (5) are needed to...
explore whether agents that increase insulin sensitivity, especially in patients with insulin-resistant T1D, reduce IHD risk.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References
2. Fahrmann ER, Adkins L, Driscoll HK. Modification of the association between severe hypoglycemia and ischemic heart disease by surrogates of vascular damage severity in type 1 diabetes during ~30 years of follow-up in the DCCT/EDIC study. Diabetes Care 2021;44:2132–2139