



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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Fahrman et al. (1) reported that, in the 1,441 subjects with type 1 diabetes (T1D) included in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study cohort (none of whom had previous cardiovascular events), the presence of at least one event of severe hypoglycemia (SH) increased the risk of ischemic heart disease (IHD) (death, silent/nonfatal myocardial infarction, revascularization, and confirmed angina) in those patients with higher baseline surrogates of microvascular damage (diabetes duration or steps on the DCCT Early Treatment Diabetic Retinopathy Study severity scale and Diabetes Complication Severity Index) during a roughly 30-year follow-up period. Their analyses did not take into account the potential role of baseline insulin resistance (IR) as a predictor of IHD events. However, when IR was assessed through the equation for the estimation of the glucose disposal rate (the lower the estimated glucose disposal rate, the higher the IR) in the DCCT cohort, it

was found to be an independent predictor of the development of retinopathy, nephropathy, and cardiovascular events (angina, fatal and nonfatal myocardial infarction, coronary revascularization, and major electrocardiographic events) over a 9-year follow-up period, introducing the concept of double diabetes with potential interest for a better phenotyping of patients with T1D in routine clinical practice (2). That equation includes only three clinical variables (hypertension, HbA<sub>1c</sub>, and obesity) and had been derived from hyperinsulinemic-euglycemic clamp studies by the Pittsburgh Epidemiology of Diabetes Complications (EDC) study group some years before. Using that equation in patients with T1D of the EDC study (none of whom had previous coronary artery events), IR was an independent predictor of hard coronary artery disease end points (death, nonfatal myocardial infarction or major Q waves in the electrocardiogram, revascularization procedures, or angiographic stenoses  $\geq 50\%$ ) after a 10-year follow-up period (3). Likewise, in an Italian cohort of patients

with T1D (5.3% with previous cardiovascular events), IR was also an independent predictor of coronary artery disease events (myocardial infarction and revascularization) over a 10-year follow-up period (4). IR assessed with that equation was also reported to be independently associated with silent myocardial ischemia (diagnosed by stress myocardial perfusion gated single-photon emission computed tomography) in a cross-sectional study of patients with T1D and no previous cardiovascular events (5). Of note, Fahrman et al. (1) reported that individuals with IHD events had higher levels of systolic blood pressure, HbA<sub>1c</sub>, and BMI and that higher baseline insulin doses (a crude measure of IR) were associated with higher risk of IHD events as well. All these results would support that IR should have been taken into account when evaluating the potential role of SH in IHD event development. Consequently, we suggest that providing information on IR in the study by Fahrman et al. could be of great interest to gain more insight into the role of SH episodes in the development

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of IHD events and to improve the phenotyping of subjects with T1D at the highest risk of developing IHD events in routine clinical practice.

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