COMMENTS AND RESPONSES

Comment on: Gruden et al. Severe Hypoglycemia and Cardiovascular Disease Incidence in Type 1 Diabetes: The EURODIAB Prospective Complications Study. Diabetes Care 2012;35:1598–1604

Marga Giménez, md
Ignacio Conget, md, phd

From the Diabetes Unit, Endocrinology Department, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBER de Diabetes y Enfermedades Metabólicas asociadas (CIBERDEM), Hospital Clínic i Universitari, Barcelona, Spain.

Corresponding author: Ignacio Conget, iconget@clinic.ub.es.

DOI: 10.2337/dc12-1248

We have read with a lot of interest the article recently published in *Diabetes Care* by Gruden et al. (1) suggesting that severe hypoglycemic episodes in patients with type 1 diabetes (T1D) do not increase the risk of cardiovascular disease (CVD). As the authors mentioned in the article (citing one of our previous papers published in *Diabetes Care*), a deleterious role of hypoglycemia in not only inflammatory and endothelial markers but also in preclinical atherosclerosis has been reported consistently (2,3). In addition to this, although with substantial limitations related to the intrinsic design of the study, more recently a retrospective analysis of a large T1D subjects' database from a national registry on continuous subcutaneous insulin infusion pointed to a higher prevalence of CVD in patients with a history of repeated episodes of hypoglycemia (4).

The data reported from the EURODIAB Prospective Complications Study is of tremendous value in order to clarify if hypoglycemia could be a potential aggravating factor for atherosclerosis in T1D (1). However, although the results do not support that hypoglycemia increases the risk of CVD in subjects with T1D, in our modest opinion there is still a place for debate. Gruden et al. were well aware of several limitations of the study, and these were included in the discussion. Data on hypoglycemia relied on self-reported information obtained from questionnaires and this can be important and underestimate the incidence of this complication, especially in those nonsevere episodes that may repeatedly impact on the risk for CVD. The prospective analysis on the incidence of CVD was based on the number of severe hypoglycemic episodes reported just 12 months before obtaining baseline data. The authors also mentioned a limitation related to identifying information concerning the cause of death. Considering all of this and cautiously revising data from Table 1, differences of nonfatal CVD incidence during the follow-up (6.8, 7.2, and 10.8%; 0, 1–2, and 3+ number of episodes of severe hypoglycemia, respectively) were nearly significant ($P = 0.05$) (1). Moreover, when comparing the data from nonfatal CVD incidence in those without severe hypoglycemia with data from those more affected by this complication (+3 episodes), this difference raises statistical significance (6.8 vs. 10.8%, $P = 0.03$).

Finally, we agree with the authors that we need further studies providing unbiased data in order to definitely deal with the hypothesis that T1D hypoglycemia increases the risk of CVD (alternative hypothesis). As Gruden et al. mentioned (1), the use of continuous glucose monitoring could be of help, but results from datasets (severe and nonsevere hypoglycemia) collected from previous landmark studies may also provide relevant information (5). In the meantime, we modestly think that the "null hypothesis" should be considered with caution.

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

References

1. Gruden G, Barutta F, Chaturvedi N, et al. Severe hypoglycemia and cardiovascular disease incidence in type 1 diabetes: the EURODIAB Prospective Complications Study. Diabetes Care 2012;35:1598–1604
2. Giménez M, Gilabert R, Monteagudo J, et al. Repeated episodes of hypoglycemia as a potential aggravating factor for preclinical atherosclerosis in subjects with type 1 diabetes. Diabetes Care 2011;34:198–203
3. Gogitidze Joy N, Hedrington MS, Briscoe VJ, Tate DB, Ertl AC, Davis SN. Effects of acute hypoglycemia on inflammatory and pro-atherothrombotic biomarkers in individuals with type 1 diabetes and healthy individuals. Diabetes Care 2010;33:1529–1535
4. Giménez M, López JJ, Castell C, Conget I. Hypoglycaemia and cardiovascular disease in Type 1 Diabetes. Results from the Catalan National Public Health registry on insulin pump therapy. Diabetes Res Clin Pract 2012;96:e23–e25
5. Kilpatrick ES, Rigby AS, Atkin SL, Frier BM. Does severe hypoglycaemia influence microvascular complications in Type 1 diabetes? An analysis of the Diabetes Control and Complications Trial database. Diabet Med 2012;29:1195–1198