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 COMMENTS AND  
 RESPONSES
 

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**Response to  
 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**

**W**e thank Dr. Giménez and Dr. Conget for their comments (1) on our article, recently published in *Diabetes Care* (2). We acknowledge that our study has several limitations, as it was stated in the discussion, and that the “null hypothesis” should be accepted with caution. In addition, we agree that further large prospective epidemiological studies in type 1 diabetic patients are needed to offer a definite answer on this relevant topic. On the other hand, we believe that existing clinical/epidemiological data in type 1 diabetic patients do not convincingly support the hypothesis of a role of hypoglycemia in cardiovascular disease. The study by Giménez et al., showing evidence of preclinical atherosclerosis in patients with frequent

hypoglycemic episodes (3), was extremely intriguing and prompted us to address this issue in the EURODIAB study. However, this work also has some limitations, such as the small number of recruited patients (25 case subjects vs. 20 control subjects) and the relatively short time of observation for group allocation (8 weeks). In the recent retrospective analysis quoted by Giménez et al. (4), cardiovascular disease prevalence was greater in patients with a history of repeated episodes of severe hypoglycemia; however, in logistic regression analysis the association between cardiovascular disease and severe hypoglycemia was not statistically significant after inclusion of age and diabetes duration into the model. Similarly, in our study differences in nonfatal cardiovascular disease incidence among hypoglycemic categories were nearly significant, as pointed out by Dr. Giménez; however, in logistic regression analysis severe hypoglycemia was not independently associated with nonfatal cardiovascular disease (3). There are clear additional differences in patients with frequent severe hypoglycemia episodes; as such older age, longer diabetes duration, and lower HbA<sub>1c</sub>, and any potential effect of severe hypoglycemia on cardiovascular outcomes can easily be over- and underestimated in this group. Therefore, results from logistic regression analysis, which allows control for confounding variables, appear more reliable. However, the lack of an independent association between severe hypoglycemia and cardiovascular disease should not lead to underestimate the possible risk of severe hypoglycemia in young type 1 diabetic patients by clinicians as this issue is still, as stated by Dr. Giménez, open to debate.

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