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LETTERS TO THE EDITOR

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Cardiovascular prevention in high-risk patients with type 2 diabetes mellitus: when to start it?

We have read with great interest the article by Mellbin *et al.*[1] that reported an increased risk of non-fatal cardiovascular events in diabetic patients on insulin treatment with myocardial infarction. This epidemiological analysis also underlines the safety of the oral glucose-lowering agents in these patients, and found that metformin administration was related to a lower cardiovascular risk. The authors highlight the fact that the differences in the risk of non-fatal cardiovascular events between insulin and oral glucose-lowering agents cannot be explained by a less efficient glycaemic control by insulin, since the analysis was adjusted for updated glucose values; however, although this asseveration is precise, there are other important confounding covariates that could have biased the observed results. Specifically, it should be noted that the group of patients on insulin therapy had a significantly longer diabetes duration compared with patients on non-insulin-based therapy (10.4 ± 8.9 vs. 4.4 ± 5.7 years, $P < 0.0001$). Although the study accurately adjusted for the effects of updated glucose levels on cardiovascular outcomes, it failed to discard the influence of chronic hyperglycaemia in the cardiovascular risk of patients on insulin treatment.

Chronic hyperglycaemia is related to the generation of advanced glycation endproducts (AGEs), which have been accused of being involved in the development of diabetic complications.[2] The accumulation of AGEs is associated with an increased generation of reactive oxygen species (ROS) and reduced production of nitric oxide by the nitric oxide synthases (NOS).[3] Delayed insulin treatment has been shown to fail to normalize the elevated serum AGE concentrations in diabetic rats, and an irreversible nitrergic degeneration as well as a loss of nitrergic function occur in these animals even when they are made euglycaemic by treating them with insulin.[3] These results suggest that AGEs rather than hyperglycaemia *per se* are responsible for ROS formation and tissue injury in diabetes later phases.

In humans as in animals, the accumulation of AGEs could participate in the development of vascular dysfunction and consequently cardiovascular disease. Because of this, the cardiovascular risk of a diabetic subject is directly related to the duration of diabetes. Furthermore, the efficacy of insulin therapy in reducing cardiovascular risk could also be affected by the duration of diabetes.

Long-term clinical trials of intensive glucose control with insulin in type 2 diabetes have not been powered enough to detect a cardiovascular benefit. However, one ongoing large clinical trial, the ORIGIN study, will allow us to establish whether providing sufficient basal insulin (as insulin glargine) to safely achieve fasting normoglycaemia reduces the incidence of cardiovascular events in high-risk patients with type 2 diabetes mellitus.[4] Because baseline glycated haemoglobin levels in this study are $\leq$9%, and because 18% of participants did not have pre-existing diabetes, the results of this trial will allow us to differentiate the effects of insulin on cardiovascular risk according to diabetes duration. Until we have these results, early insulin treatment should be encouraged in diabetic subjects, especially in those at high risk of developing cardiovascular disease.

References

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We are grateful for the attention our article on the potential drawback of insulin in patients has attracted, most recently in the letter to the Editor by Drs Garcia and Lopez-Jaramillo. This debate may encourage further efforts to study the proper use of this and other glucose-lowering drugs and serves as an incitement to conduct better trials not only addressing the glucose-lowering potential of these drugs but also and importantly their impact on cardiovascular morbidity and mortality.

We agree with the point raised by the authors of the letter that duration of diabetes certainly may be an important factor for the outcome of our study. In the DIGAMI 2 trial, patients with insulin treatment did indeed have a longer duration of their disease.[1] Looking only at patients with newly instituted insulin at discharge, where of a majority were randomized to insulin, the difference was still