Low blood glucose levels in type 2 diabetes: a lot more to come?

The primary composite end-point was the same as in the EMPA-REG OUTCOME study. After 3.8 years of follow-up, the primary outcome was significantly lower in the liraglutide group than in the placebo group, due to fewer CV and all-cause deaths in the interventional group. In both trials, despite better glycemic control in interventional groups, hypoglycemia episodes were not more frequent than in placebo. Interestingly, in the LEADER trial there have been even fewer hypoglycemia incidents in patients on liraglutide than in those on placebo. A reduction in the number of hypoglycemia episodes may be one of the mechanisms accounting for the improvement of CV prognosis, caused by those new antidiabetic drugs. In the light of the data from both trials, the current guidelines were already revised in some countries.

Although insulin therapy is an inevitable treatment in most patients with type 2 diabetes, no trial has demonstrated a reduction in mortality rates resulting from insulin treatment. Recently, preliminary data from the DEVOTE study has shown a significant 40% reduction in the number of severe hypoglycemia episodes, as well as a 54% reduction in the number of nocturnal hypoglycemia incidents, in patients treated with a new long-acting insulin analog (degludec) as compared to insulin glargine. Of note, this was associated with a trend (9%) toward fewer major CV events.

Diabetes is associated with increased platelet aggregation, thrombin generation, and unfavorable fibrin clot properties. Interestingly, not only hyperglycemia but also hypoglycemia is associated with prothrombotic changes and compact fibrin clot formation, which is more resistant to lysis. Moreover, it has been recently shown that in type 2 diabetes low glucose level (<4.5–5 mmol/l), which does not fit the criteria for hypoglycemia, is also associated with dense and resistant to lysis fibrin clot, enhanced thrombin generation, and a trend to increased platelet aggregation. Those results suggest that active monitoring for low glucose levels preceding hypoglycemia might be worth considering, similarly to screening for prediabetes, especially in the highest-risk patients.
To sum up, available new data strengthen the conclusion that besides the treatment of hyperglycemia, avoidance of hypoglycemia should be regarded as an additional therapeutic target in optimal antidiabetic treatment.

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