Non-Severe Hypoglycemia Predicts Increased Risk of Subsequent Serious Adverse Events in Patients With Type 2 Diabetes

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Aim

• It is well-known that higher rates of non-severe hypoglycemic episodes (NSHEs) associate with a greater risk of severe hypoglycemic episodes in patients with type 1 diabetes.

• We aimed to investigate whether a similar association existed in patients with type 2 diabetes (T2D).

• We also aimed to investigate the association between non-severe hypoglycemia and other adverse events time to first Major Adverse Cardiovascular Event (MACE).

Methods

• We used data from the LEADER trial, a cardiovascular outcomes trial with patients randomised to either the OJ-PA or insulin glargine or placebo.

• The LEADER trial included 9440 T2D patients at high risk of cardiovascular events, pre-existing CV-disease (CVE) or risk factors for CV-disease (19%)(Table 1) The trial information and baseline data has previously been published in detail.

• During the trial period of 15,563 patients years of observation (median follow up of 3.8 years), a total of 27,916 NSHEs were registered (28.1 ± 40.9 NSHEs per patient).

• There were 433 severe hypoglycemic episodes, 1,602 first time MACE, 497 cases of CV death and 828 cases of all-cause mortality.

• In the sensitivity analysis, we explored if the annual rate of NSHEs was associated with time to first severe hypoglycemic episode, time to first MACE, time to CV death and time to all-cause mortality.

• A Cox proportional hazards model was used, adjusted for dependent covariate with three levels; 
  - Group A: <2 NSHEs per year
  - Group B: 2-11 NSHEs per year
  - Group C: ≥12 NSHEs per year

The rate for severe hypoglycemia was increased - also when the annual event rate was 2 per year.

• As the findings are limited to observational associations it is possible that even non-severe hypoglycemia is associated with acute and persistent prothrombotic effects illustrating a possible mechanism by which hypoglycemia can increase CV risk.

• Moreover secondary analysis of a large landmark trials has consistently shown the association between hypoglycemia and increased CV risk.

• As the findings are limited to observational associations it is therefore continuously discussed if hypoglycemia is a marker or mediator of the associated CV risk.

• Our results supports the findings that there is a strong association between the rate of non-severe hypoglycaemia and adverse outcomes, consistent within multiple sensitivity analysis.

• Independence of causality, reducing the risk of any hypoglycemia by lifestyle intervention or pharmacological solutions may be beneficial for any patient – including those at high CV risk.

Results

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Group</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.5 (8.0)</td>
<td>64.1 (8.0)</td>
<td>64.0 (8.0)</td>
<td>63.0 (8.0)</td>
</tr>
<tr>
<td>Male, %</td>
<td>49%</td>
<td>50%</td>
<td>49%</td>
<td>48%</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.5 (6.3)</td>
<td>32.79 (6.35)</td>
<td>31.9 (6.01)</td>
<td>31.54 (6.17)</td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>12.8 (8.0)</td>
<td>11.9 (7.6)</td>
<td>14.5 (8.4)</td>
<td>16.2 (8.5)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.6 (1.4)</td>
<td>7.3 (1.4)</td>
<td>7.6 (1.4)</td>
<td>7.8 (1.4)</td>
</tr>
<tr>
<td>Peripheral neuropathy, %</td>
<td>13%</td>
<td>14%</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>24%</td>
<td>25%</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>45%</td>
<td>46%</td>
<td>44%</td>
<td>46%</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>32%</td>
<td>32%</td>
<td>31%</td>
<td>33%</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Chronic kidney disease, %</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>36%</td>
<td>35%</td>
<td>36%</td>
<td>37%</td>
</tr>
</tbody>
</table>

The sensitivity analysis was investigated with three sensitivity analysis:

1. Adjusting the primary analysis for baseline information (i.e., baseline HbA1c, diabetes duration, age and insulin treatment) were assessed.

2. Rather than updating the time-dependent covariate at the time of each event it was updated in windows of size 100 days. The NSHE event rate at the closure of each window is used as covariate value for the following window. The fill for each value of the time-dependent covariate is used to investigate the association.

3. The first year of observation is used to categorize all patients according to group A, B, or C. The subsequent follow-up time beyond the first year is used to investigate the association with a Cox regression model with two covariates with constant values.

The first sensitivity analysis investigated if a high annual NSHE rate can be moderated through selected baseline characteristics.

The second sensitivity analysis investigated the dependence of the results toward the method of adjusting for the dynamic NSHE rate. The performance was assessed with a range of window sizes.

The third sensitivity analysis was performed to avoid the time-dependent covariate but instead categorize patients at a given follow-up time and use this as constant covariate throughout the analysis. In this analysis the number of events (severe hypoglycemia, MACE, CV death) is notably reduced.

Conclusion

• Higher rates of NSHE was associated with a higher rate of severe hypoglycemia, MACE, CV death and all-cause death in patients with T2D (Figure 2).

• For MACE, CV death and all-cause mortality the association was driven by patients with an annual event ≥2.

• The rate for severe hypoglycemia was increased – also when the annual NSHE event rate was ≥2 per year.

• The sensitivity analyses support the primary findings. In the third sensitivity analysis the total number of events is notably reduced, which affects the CI but the point estimates are consistent. (Figure 3).

Discussion

• There is an increasing amount of evidence pointing to hypoglycemia as a detrimental factor in development of complications to both type-1 and type-2 diabetes (4).

• Previously a number of effect pathways has been demonstrated, one being that even non-severe hypoglycemia is associated with acute and persistent prothrombotic effects illustrating a possible mechanism by which hypoglycemia can increase CV risk.

• Moreover secondary analysis of a number of landmark trials has consistently shown the association between hypoglycemia and increased CV risk.

• As the findings are limited to observational associations it is therefore continuously discussed if hypoglycemia is a marker or mediator of the associated CV risk.

• Our results supports the findings that there is a strong association between the rate of non-severe hypoglycaemia and adverse outcomes, consistent within multiple sensitivity analysis.

• Independence of causality, reducing the risk of any hypoglycemia by lifestyle intervention or pharmacological solutions may be beneficial for any patient – including those at high CV risk.