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. [1]
- 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†), time to cardiovascular (CV) death, and time to all-cause mortality.

Methods

- We used data from the LEADER trial; a cardiovascular outcomes trial with patients randomized to either the GLP1-RA liraglutide or placebo.
- The LEADER trial included 9340 T2D patients at high risk of cardiovascular events; pre-existing CV-disease (81%) or risk factors for CV-disease (19%). [Table 1] The trial information and baseline data has previously been published in details.[2,3]
- During the total trial period of 35,563 patient years of observation (median follow-up of 3.8 years), a total of 27,933 NSHEs were registered (BS <3.1 mmol/L). There was 433 severe hypoglycemic episodes, 1,302 first 3-point-MACEs, 497 cases of CV death and 828 cases of 'all-cause mortality'.
- In this secondary 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 randomized treatment arm, and annual rate of NSHE as a time-dependent covariate with three levels;
    - Group A: <2 NSHEs per year (reference)
    - Group B: 2-11 NSHEs per year
    - Group C: ≥12 NSHEs per year
- The time-dependent covariate was updated at each NSHE event time. The association between NSHE and outcome is estimated with Hazard ratios (HR).
- The robustness of the results was investigated with three sensitivity analysis:

1. adjusting the primary analysis for baseline information (sex, baseline HbA_{1c}, diabetes duration, age and insulin treatment)
2. Rather than updating the time-dependent covariate at the time of each event it is 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 HR 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-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 event rate can be moderated through selected baseline characteristics.
- The second sensitivity analysis investigated the dependence of the results toward the method of accounting for the dynamic NSHE rate. The analysis was performed 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-deaths) is notably reduced.

Results

- Baseline characteristics according to an exclusive A-C grouping where patients are categorized according to their highest observed annual NSHE rate is similar with regard to age, BMI and gender distribution. Patients with risk time in group C had lower baseline HbA_{1c}, longer duration of diabetes and less likely to be insulin naïve. [Table 1]

Table 1 Baseline characteristics

	Overall	Group A	Group B	Group C
N	9340	6723	1509	1101
Age, years	64.3 (7.2)	64.19 (7.26)	64.67 (7.21)	64.36 (7.02)
BMI, kg/m^2	32.5 (6.3)	32.79 (6.35)	31.9 (6.01)	31.54 (6.17)
HbA1c (%)	8.7 (1.5)	8.72 (1.55)	8.73 (1.52)	8.48 (1.38)
Female sex (%)	36%	35%	36%	37%
Diabetes duration, years	12.8 (8.0)	11.9(7.6)	14.5(8.4)	16.2(8.5)
Existing CVD/CKD (%)	81%	80%	83%	85%
CVD risk factors (%)	19%	20%	17%	15%
Insulin naive (%)	55.5%	61%	44%	36%

Table notes: Baseline characteristics for the total trial population and those experiencing a NSHE annual event rate >12 (group C), for those experiencing an annual event rate>2 but not >12 at any time during trial (group B) and for with n annual event rate <=2 during trial (group A). Due to incomplete baseline information 7 subjects were not included in the table.

Figure 2 Hazard ratios (95% CI) for severe hypoglycemia, MACE, CV death and all-cause death by NSHE rate groups.

Key Result

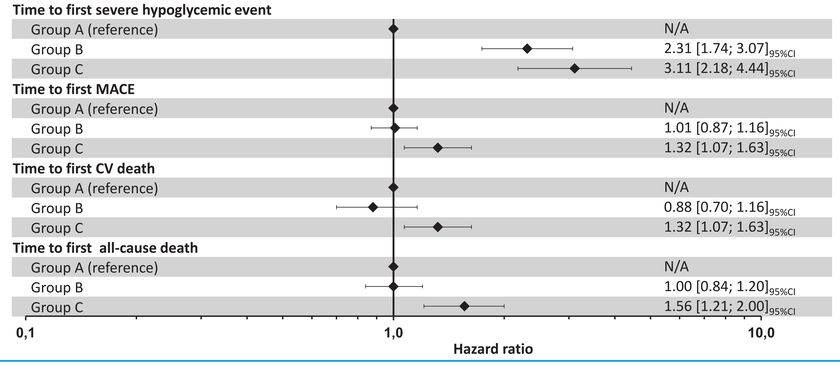
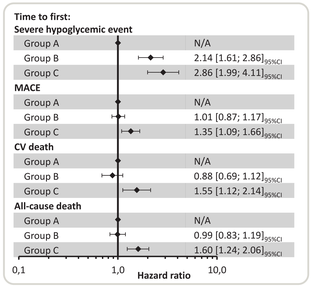
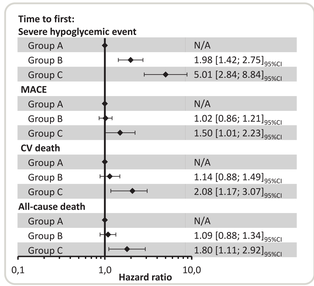


Figure 3 Sensitivity analysis (1-3)

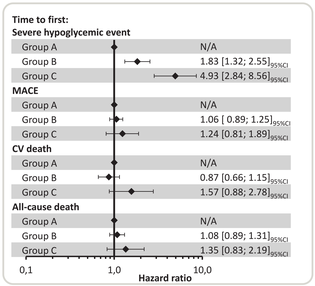
Sensitivity analysis 1: primary analysis adjusted for baseline information



Sensitivity analysis 2: 100 days of observation "windows"



Sensitivity analysis 3: Patients categorized by NSHE annual event rate in first 12 months



- 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 ≥12.
- 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 hypoglycaemia 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.[5]
- Moreover secondary analysis of a number of large landmark trials has consistently shown the association between hypoglycemia and increased CV risk. [6]
- 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 hypoglycemia and adverse outcomes, consistent within multiple sensitivity analysis.
- Independent 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.

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 2-3);
- Our results suggest that in this T2DM population, a high rate of NSHEs is associated with serious adverse events and should be avoided.

†3-point MACE (CV death, non-fatal MI, non-fatal stroke)

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References: **(1)** Kovatchev et al, Diabetes Care 21:1870-1875, 1998 **(2)** Marso et al. Am Heart J. 2013 Nov;166(5):823-30 **(3)** Marso et al. N Engl J Med 2016; 375:311-322 **(4)** International Hypoglycaemia Study Group. Lancet Diabetes Endocrinol 7:385-396, 2019 **(5)** Chow et al. Diabetes Care 41:2625-2633, 2018 (6) Bonds et al. BMJ 340:b4909, 2010