Reviewer's report

Title: Hypoglycaemia incidence and the risk of vascular events - an analysis of the prospective DiaRegis registry

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Reviewer: Birger Thorsteinsson

Reviewer's report:

The manuscript reports the results of a population-based, prospective, observational registry study of the occurrence of events of hypoglycaemia of different degrees of severity in patients with type 2 diabetes treated with oral hypoglycaemic agents and describes risk predictors of hypoglycaemia (any degree of severity). The authors also report an association between occurrence of hypoglycaemia and risk of incident vascular disease. The authors have previously reported data concerning recalled hypoglycaemia (called anamnestic hypoglycaemia by the authors) in this patient group.

Prospective reports on occurrence of hypoglycaemia in large populations-based studies are scarce but warranted. The paper therefore addresses an important, clinically relevant topic that has been under-studied to date.

1) Title: Imprecise, suggests e.g. “Incidence and predictors of hypoglycaemia in type 2 diabetes: An analysis of the prospective DiaRegis registry”. Leave out “risk of vascular events” (see below).

2) Abstract:
   a) The present title does not match the aim in the Abstract (but the suggested title does).
   b) Results: I suggest that all data about incident hypoglycaemia and risk of vascular disease is deleted from the present report (may be reported in another paper).
   c) Line 3: “complication” should be “adverse effect”
   d) Line 4: “incidence rates” of what?
   e) Line 6-8: poor language, suggests e.g. “DiaRegis is a prospective German registry including 3810 patients with type 2 diabetes referred to treatment intensification because of insufficient glycaemic control on one or two oral antidiabetics.”

3) Background:
   a) Page 3, line 3-5: This statement needs a reference. Hypoglycaemia is defined as blood glucose below 4 mmol/l by ADA and recently by EMA (and below 3 mmol/l in the old EMA definition). The choice of cut-off for hypoglycaemia therefore needs to be discussed.
b) The present title does not match the aim in Background (page 3, line 11-15) (but the suggested title does).

c) Page 3, line 6: “sympathetic” should be “hormonal”.

d) Page 3, line 8-9: A “discussion” with only one reference is insufficient. I suggest “It is presently discussed if severe hypoglycaemia a marker of an increased risk of death and other adverse clinical outcomes rather than a direct cause (ACCORD reference). The presence of coexisting conditions could increase a patient’s vulnerability to both severe hypoglycaemia and an adverse clinical outcome in the absence of a direct causal link between the two (Cryer, Am J Med 2011; 1289: 993-995 and Boucai et al., Am J Med 2011; 1289: 1028-1035).”

e) Page 3, 2nd paragraph: Rephrase the first lines. The cohort is not prospective, the study is.

4) Methods:

a) Much of this section is a repetition of a similar section in Tschöpe et al, Cardiovasc Diabetol 2011; 10: 66. However, important information is still missing. What kind of information is found in the DiaRegis? How did the physician know about DiaRegis? Who decides if a patient does not fulfil the inclusion criteria – the authors or the treating physician? Patients with surgery and emergencies were excluded – by which criteria? This should all be mentioned as well as the total number of patients in DiaRegis.

b) Hypoglycaemia reporting: Who reported (patient/doctor)? It is unclear how hypoglycaemia was reported (how close to the incident), how often (once a month/when it happened/or?), how were episodes validated (Whipple’s triad?), especially the episodes of severe hypoglycaemia.

c) How is anamnestic hypoglycaemia defined? All events? Totally, ever in lifetime with diabetes, last year or?

d) How is blood glucose self-monitoring defined? As yes/no, as measurements per week, or? The frequency of mild hypoglycaemia in particular is dependent on BG-measurement frequency. This should be discussed.

e) How is clinically relevant depression defined?

f) Page 5, line 3-8: Apparently only variables significantly associated with occurrence of hypoglycaemia in univariate analyses were entered in the multivariate analysis. However, we need to know all variables analysed univariately. Other possible risk predictors may have turned out to be insignificant at univariate analyses, as indicated in Discussion, page 9, line 15: “out of a number of variables considered to …” It is not stated whether variables well-known to confer risk of hypoglycaemia like duration of diabetes, dementia and kidney insufficiency were analysed. After all, duration of diabetes has apparently been included into the multivariate analysis, since it is stated that patients incident hypoglycaemia have had diabetes for longer than those without hypoglycaemia (page 5, line 18).

g) Hypoglycaemia unawareness is not mentioned but has been measured
according to Bramlage et al, Cardiovasc Diabetol 2010;9:53, Table 1. This parameter is a major risk indicator of severe hypoglycaemia in type 1 and insulin-treated type 2 diabetes. Was this parameter included in the univariate analyses?

5) Results:

a) Page 5, line 11-13: 463 non-participants are also mentioned in Methods, page 4, line 5-6. I suggest that they are only mentioned in the Methods section.

b) Data on the distribution of hypoglycaemic events (all types) are needed. How many had more than one episode?

c) Table 1:

i) Are these data at baseline or after one year of treatment in your programme? If the data are entry data it is incorrect to include patients on injectable therapy.

ii) Percentages in the pharmacotherapy section exceed 100% (109 vs. 106%) in both groups. Why?

iii) Divide Table 1 into two tables so that information regarding pharmacotherapy is in a separate table. A table on pharmacotherapy at start and end of study would help.

d) Figure 1:

i) In Figure 1 retrospectively and prospectively recorded hypoglycaemic events are compared. How good is recall of hypoglycaemia in the present group of elderly patients, especially concerning mild hypoglycaemia. Under-reporting may be present, should be discussed.

ii) A table is inserted below Figure 1. It appears truncated, missing data on events leading to admission to hospital. No. of episodes per patient is given, is it per year?

iii) Symptomatic mild episodes of hypoglycaemia without concomitant blood glucose measurement may be more prevalent than events with measured blood glucose. Do you have any data?

iv) Page 5, line 25-27: These figures cannot be seen in Figure 125. Thus, the proportion of patients with severe hypoglycaemia stated to be 0.5% in Figure 1. However, in Figure 1 the number is 0.1%.

e) Figure 2:

i) The Forest plot only includes parameters significantly different from 1. For comparison, all parameters included in the multivariate analysis should be included in the plot.

ii) What is the significance of the red and blue colours?

f) Figure 3:

i) Delete these data from the paper.

6) Discussion:

a) Needs to be more concise. A section regarding the study’s limitations and strengths is warranted.
b) 1st paragraph: No need to repeat figures, the paragraph can be deleted.
c) It should be discussed why significant risk predictors at multivariate analyses differ when hypoglycaemia data are collected retrospectively (low HbA1c, stroke/TIA, heart failure, use of SU) (Cardiovasc Diabetol 2011;10:66) versus prospectively (previous hypoglycaemic episodes, retinopathy, depression, use of insulin, blood glucose measurement)
d) In particular the finding that SU treatment is hypoglycaemia-neutral at prospective versus retrospective recording (page 7, line 10-12) should be stressed and discussed in more detail and mentioned in the abstract as well. This is an important clinical message, which will also demonstrate that the authors are unbiased.
e) The study is a population study or a cohort study. In Bramlage et al is stated “the sampling strategy should thus provide a representative dataset for the description of oral antidiabetic treatment in Germany”. How representative are the participants as compared with the German population of patients with type 2 diabetes?
f) Thoughts on the effect of setting the hypoglycaemic blood glucose threshold at 3 or 4 mmol/l are welcome.
g) Did doctors treat patients with retinopathy more intensively compared to the patient without retinopathy to prevent progression.
h) Page 9, line 25: ITTP should be spelled out.
i) The paragraph “Prognostic implications” should be deleted.
j) Page 11, line 2: “ complication” should be “adverse effect”
k) Page 11, line 6: “severe but asymptomatic hypoglycaemia” is an unfortunate and illogical mixture of nomenclature.
l) Page 11, line 2-3: “hypoglycaemia is a frequent complication when antidiabetic treatment is intensified”. Compared to ? This is not statistically supported in the paper.

7) Hypoglycaemia or hypoglycemia is used at random.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.