



Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes – A Systematic Review of the Evidence

EXECUTIVE SUMMARY

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BACKGROUND

Prevalence of type 2 diabetes is increasing at an alarming pace, fueled by the rising rates of overweight and obesity in many populations. In the VA healthcare system, the prevalence of diabetes was 20% in fiscal year 2000 and is now estimated at nearly 25%.

Although people with diabetes have a substantially increased risk of cardiovascular disease (CVD), recent trials show that intensive glucose lowering does not reduce the risk of CVD death or all-cause mortality although it reduces the risk of microvascular complications (nephropathy, retinopathy and neuropathy) and possibly non-fatal myocardial infarction. Intensive glucose control also increases the risk of hypoglycemic episodes. Several recent meta-analyses of the trials comparing intensive to conventional glucose control concluded that intensive control is associated with a 2-2.5 fold increased risk of severe hypoglycemia. The reviews however have not included smaller randomized trials, trials focused on the comparison of specific drug regimens, and non-randomized trials. We conducted the current review to provide broader insight into the incidence of, the risk factors for, and the clinical and social impact of severe hypoglycemia in adults with type 2 diabetes treated with glucose lowering medications.

The key questions were as follows: In adults with type 2 diabetes treated with one or more hypoglycemic agents:

Key Question #1: What is the **incidence** of severe hypoglycemia in adults with type 2 diabetes on one or more hypoglycemic agents?

Key Question #2: What are the **risk factors** for severe hypoglycemia in adults with type 2 diabetes on one or more hypoglycemic agents (e.g., demographics, co-morbidities, diabetes treatment regimen, other medication use, goal and achieved HbA1c)?

Key Question #3: What is the effect of severe hypoglycemia on other **outcomes** in adults with type 2 diabetes on one or more hypoglycemic agents (e.g., quality of life, mortality, morbidity, utilization)?

METHODS

We searched MEDLINE (OVID) for clinical trials and systematic reviews from 1950 to through November 2011 using standard search terms. Studies were eligible if they involved adults with type 2 diabetes, were published in the English language and reported outcomes of interest. Search terms included: hypoglycemia, hypoglycaemia, and diabetes mellitus, type 2. The search was not limited to randomized controlled trials (RCTs). We obtained additional articles from a search of the Cochrane Library, other systematic reviews, reference lists of pertinent studies, reviews, editorials and expert consultation. We defined severe hypoglycemia as an episode with typical symptoms resolving after treatment administered by another person.

Investigators and research assistants trained in the critical analysis of literature assessed for relevance the abstracts of citations identified from literature searches. Full-text articles of

potentially relevant abstracts were retrieved for further review. For Key Questions #1 and #2, we excluded studies with fewer than 500 patients or duration less than 6 months. We also excluded studies if the medications involved were not FDA approved. For Key Question #3, there were no restrictions on sample size or study duration.

Study characteristics, patient characteristics, and outcomes were extracted by investigators and trained research associates under the supervision of the Principal Investigator. We assessed study quality according to established criteria for randomized trials and non-randomized trials.

DATA SYNTHESIS

We constructed evidence tables showing the study characteristics for all included studies. Outcomes tables were organized by key question. We critically analyzed studies to compare their characteristics, methods, and findings. We compiled a summary of findings for each key question or clinical topic, and drew conclusions based on qualitative synthesis of the findings or pooled results, where appropriate. We identified and highlighted findings from veteran populations.

PEER REVIEW

A draft version of this report was reviewed by technical experts, as well as clinical leadership. Reviewer comments were addressed and our responses may be found in Appendix C.

RESULTS

We reviewed 2353 titles and abstracts from the electronic search. After applying inclusion/exclusion criteria at the abstract level, 1914 references were excluded. We retrieved 439 full-text articles for further review and another 320 references were excluded. We identified 8 references by hand searching reference lists of relevant publications resulting in a total of 127 references for inclusion in the current review.

Key Question #1. What is the incidence of severe hypoglycemia in adults with type 2 diabetes on one or more hypoglycemic agents?

Overall incidence of severe hypoglycemia was less than 1% in most of the 60 reviewed studies, particularly those of metformin monotherapy (<1%), glucagon-like peptide-1 (GLP-1) analogs (< 1%), dipeptidyl-peptidase-4 (DPP-4) inhibitors (<1%), insulin detemir (<1%), glinides (0%) and thiazolidinediones (TZDs) (<1%). Annual rates of severe hypoglycemia were greater than 1% for sulfonylureas and the following insulin preparations: neutral protamine Hagedorn (NPH), glargine, lispro and glulisine. Some of the highest rates of severe hypoglycemia were seen in trials of intensive glucose control.

We reviewed an additional 16 studies to gain a broader population-based perspective on incidence of symptomatic hypoglycemia (defined more broadly than “severe”): 13 were survey studies reporting patient-recalled rates. Eleven of these 13 asked patients to report on events in the past 6 months (N=6) to one year (N=5). In these 11 studies, patient reported incidences of

symptomatic hypoglycemia varied widely from 1% to 17%, likely due to a wide range of study designs, populations, and lengths of follow-up.

Limitations

Much of the evidence comes from reports of RCTs funded by pharmaceutical companies which enroll highly selected populations and generally do not include those at highest risk for hypoglycemia. Furthermore, the definitions of severe hypoglycemia varied among studies and there is likely substantial ascertainment bias, especially in the RCTs designed primarily to measure the benefits of specific drug regimens.

Discussion

The incidence of severe hypoglycemia ranges from 0-3% per year for adults with type 2 diabetes on hypoglycemic medications. Incidence is highest in studies of people on insulins, sulfonylureas and regimens targeting intensive control of hemoglobin A1c (HbA1c) levels. Risk is negligible for people on metformin, GLP-1 analogs, DPP-4 inhibitors, glinides and TZDs. The incidence was more than 2-fold greater among patients undergoing intensive control compared with conventional control. The most important limitation of the data is that they were mostly derived from industry funded randomized trials of highly selected populations. A review of survey data from more representative populations suggests that the incidence of symptomatic hypoglycemia may be more common than reported in these trials.

Key Question #2. What are the risk factors for severe hypoglycemia in adults with type 2 diabetes on one or more hypoglycemic agents (e.g., demographics, co-morbidities, diabetes treatment regimen, other medication use, goal and achieved HbA1c)?

We identified 14 articles from 12 studies that reported multivariate adjusted risk factor analyses for severe hypoglycemia in adults with type 2 diabetes on hypoglycemic medications. Since these varied considerably with respect to risk factors evaluated (and their definitions), populations studied, and lengths of follow-up, the data were considered unsuitable for pooling. Transient causes (e.g., missed meal, excess exercise, alcohol use, acute infection) were not included.

Independent risk factors for severe hypoglycemia in persons with type 2 diabetes on hypoglycemic medication include: intensive glycemic control, history of hypoglycemia, renal insufficiency, history of microvascular complications, longer diabetes duration, lower education level, African American race and history of dementia. Gender, age and BMI are not consistently associated with risk, although in the two largest studies, higher age and lower BMI were significantly associated with higher risk.

Limitations

We were unable to pool results across studies due to the heterogeneity of the study designs, analytical methods and risk factors assessed. Furthermore, the data are relatively sparse and almost certainly reflect publication bias.

Discussion

The literature in this area is relatively sparse. We did not identify any other systematic reviews that evaluated risk factors for severe hypoglycemia in people with type 2 diabetes, although our findings are generally consistent with what has been summarized elsewhere. The most important limitation of the data is that there is likely publication bias since negative analyses are less likely to be published. In addition several potential risk factors (e.g., recent hospital discharge, smoking status, polypharmacy, alcohol consumption) have not been adequately evaluated.

Key Question #3. What is the effect of severe hypoglycemia on other outcomes in adults with type 2 diabetes on one or more hypoglycemic agents (e.g., quality of life, mortality, morbidity, utilization)?

We identified 53 studies (in 59 articles) that provided outcomes data from patients who experienced severe hypoglycemia. Overall, we found good evidence for an increased risk of the following outcomes: all-cause mortality, neurological events (other than non-fatal stroke), hospital and emergency department utilization and decreased quality of life. We found limited data about non-fatal MI, non-fatal stroke, cognitive decline, motor vehicle accidents, falls and traumatic injuries, work productivity and other medical service utilization.

Limitations

Few studies that address outcomes of severe hypoglycemic episodes include appropriate control groups. In addition, many outcomes of interest were not widely reported.

Discussion

Episodes of severe hypoglycemia may be a marker of serious illness and observed clinical outcomes may be due to illness rather than severe hypoglycemia. Similarly, it is unclear whether severe hypoglycemia contributes to cognitive decline or whether individuals experience more episodes of severe hypoglycemia as a result of cognitive decline.

FUTURE RESEARCH RECOMMENDATIONS

Key Question #1 and Key Question #2: Larger population-based prospective studies of people on a variety of hypoglycemic agents that employ accurate methods for ascertaining incidence of severe hypoglycemia should be performed. Studies should control for or stratify outcomes by important patient, disease and comorbidity factors including: age, gender, race/ethnicity, socio-economic and marital status, disease duration and severity (e.g., HbA1c level, presence or absence of diabetic complications).

Key Question #3: Future studies of outcomes associated with severe hypoglycemia should be prospective, use a uniform and generally accepted definition of severe hypoglycemia and include as controls people with medication-treated diabetes who have not experienced severe hypoglycemia. Also, studies should clearly distinguish between short-term or episode-related versus long-term consequences.