Diabetes journals

Severe hypoglycaemia: A predictor of adverse CV outcomes

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In people with diabetes, a major aim of glycaemic control is to prevent the short- and long-term complications of the disease. Intensive treatment for T2D can result in hypoglycaemia, which is a major barrier to intensifying treatment and achieving the benefits of good glycaemic control. Furthermore, results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial showed that hypoglycaemia related to the use of antidiabetes medications was associated with the excess mortality (Dluhy and McMahon, 2008). A *post hoc* analysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterex and Diamicron Modified Release Controlled Evaluation) trial data also found a strong association between severe hypoglycaemia and a greater risk of vascular and non-vascular outcomes (Zoungas et al, 2010). A variety of plausible biological mechanisms have been suggested in support of the clinical trial outcomes (Desouza et al, 2010).

> ***"The study results demonstrated that individuals who experienced hypoglycemia during the index treatment period after the administration of a new antidiabetes drug were at an approximate two-fold risk of developing cardiovascular complications compared with controls."***

The study by Zhao et al (2012; summarised alongside) is the first to use clinical practice data to examine how hypoglycaemia affects the risk of vascular disease in people with T2D. Study participants were selected from the Veterans Integrated Service Network 16 (VISN) between 1 January 2001 and 1 September 2010; all had T2D identified by ICD-9-CM codes. The index date was defined as the first date participants commenced new antidiabetes medications (index treatment). Exclusion criteria was listed as 1-year pre-index records of hypoglycaemia, and cardiovascular and microvascular diseases. Appropriate ICD-9-CM codes identified the hypoglycaemia group within the index treatment period. A control group was composed of propensity score-matched individuals. Statistical analysis using Kaplan–Meier analysis and Cox proportional hazards regression models compared cardiovascular events, microvascular complications and all-cause death.

The study results demonstrated that individuals who experienced hypoglycaemia during the index treatment period after the administration of a new antidiabetes drug were at an approximate two-fold risk of developing cardiovascular complications compared with individuals in the control group. These observations support both prior clinical trial and observational data (Johnston et al, 2010) that indicated a strong link between hypoglycaemia and adverse outcomes in people with T2D. Furthermore, they provide additional evidence in support of the importance of avoiding hypoglycaemia.

However, as with all observational studies, important limitations must be considered, in particular the impact of possible missing data. In this study, data were not available on the duration of diabetes, duration and dose of insulin use, and timely self-monitored glucose levels. Further considerations include a lack of formal hypoglycaemia diagnostic testing reported in this study and under-reporting of hypoglycaemia. Furthermore, this patient cohort is not truly representative of the general diabetes population as it largely consists of older males.

Nevertheless, the study outcomes further support the notion that, in susceptible individuals, severe hypoglycaemia is an important determinant of adverse cardiovascular outcomes, and should therefore be closely monitored.

Desouza CV, Bolli GB, Fonseca V (2010) Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care* **33**: 1389– 94

Dluhy RG, McMahon GT (2008) Intensive glycemic control in the ACCORD and ADVANCE trials. *N Engl J Med* **358**: 2630–33

Johnston SS, Conner C, Aagren M (2011) Evidence linking hypoglycemic events to an increased risk of acute cardiovascular events in patients with type 2 diabetes. *Diabetes Care* **34**: 1164–70

Zoungas S, Patel A, Chalmers J et al; ADVANCE Collaborative Group (2010) Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* **363**: 1410–8

DIABETES CARE

Hypoglycaemia associated with higher CV risk

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 In this retrospective cohort study, the authors set out to determine the impact that hypoglycaemia has on cardiovascular events in people with T2D in clinical practice.

2 Adults with T2D (n=44 261) were selected from the Veterans Integrated Service Network 16 between January 2001 and September 2010. Following a 6-month washout period, individuals initiated a new antidiabetes medication, defined as the "index treatment" – the "index date" referred to the date on which therapy was commenced.

3 During the index treatment period, hypoglycaemia was diagnosed using ICD-CM codes. Events were recorded during the follow-up period, including cardiovascular disease (myocardial infarction, stroke, congestive heart failure and peripheral vascular disease), microvascular complications and all-cause death. Data were compared with data from propensity score-matched individuals.

4 People in the hypoglycaemia group were more likely to develop cardiovascular disease (CVD) and microvascular complications compared with the control group (P=0.0001 and P<0.001, respectively). Individuals with more than one hypoglycaemic episode were more likely to develop peripheral vascular disease than those with one episode. There was no significant between-group difference in mortality.

5 The authors concluded that hypoglycaemia is associated with higher rates of cardiovascular events in people with T2D, and should be closely monitored.

Zhao Y, Fonseca V, Campbell CR et al (2012) Impact of hypoglycaemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. *Diabetes Care* **35**: 1126–32

DIABETIC MEDICINE

Pharmacists reduce 10-year CV risk in T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Clinical guidelines recommend comprehensive management of cardiovascular (CV) risk factors in people with T2D, but this is not always achieved.

2 The authors set out to determine the effect of adding pharmacists to primary care teams on the predicted 10-year risk of CV events in people with T2D without established CV disease, and to compare the predicted 10-year risk between the UKPDS risk score and the Framingham risk score.

3 People aged between 30 and 74 years being treated for T2D in primary care clinics were randomised to an intervention group (n=102) or control group (n=93) for 1 year. The intervention group received care from pharmacists, including a complete medication review, limited physical examination, and recommendations for optimising medication management of cardiovascular factors. The control group received standard care without pharmacist involvement.

4 Baseline and 1-year characteristics were measured and the reductions in UKPDS and Framingham risk scores calculated for both groups. At 1 year, there was a statistically significant median absolute reduction in the UKPDS and Framingham risk scores in the intervention group compared with the control group (P=0.032 and P=0.048, respectively). There was also a strong correlation between the two risk scores (P<0.001).

5 The authors concluded that the addition of pharmacists to primary care teams reduced the 10-year CV risk for people with T2D without CV factors.

Ladhani NN, Majumdar SR, Johnson JA et al (2012) Adding pharmacists to primary care teams reduces predicted long-term risk of cardiovascular events in type 2 diabetic patients without established cardiovascular disease. *Diabet Med* 29 Apr [Epub ahead of print]

DIABETOLOGIA

ACCORD Lipid Study analysis

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The authors set out to characterise people with T2D at risk of fenofibrate-associated creatinine increase (FACI), and to determine whether they were at a differential risk of adverse renal or cardiovascular (CV) outcomes.

2 The ACCORD (Action to Control Cardiovasuclar Risk in Diabetes) Lipid Study randomised people with T2D who were taking simvastatin (n=5518) to either fenofibrate treatment or placebo. FACI was defined as a 20% rise in serum creatinine levels at 4 months. Renal and CV outcomes were measured in people with FACI.

3 In total, 48% of people randomised to fenofibrate developed FACI; they displayed common clinical characteristics, were more likely to have a decrease in triacylglycerol at 4 months and showed no increase incidence of renal disease or CV outcomes over time compared with controls.

4 The authors concluded that a number of clinical characteristics predict FACI and people with FACI may be more sensitive to the beneficial effects of fenofibrate whilst being at no increased risk of adverse renal or CV outcomes.

Bonds DE, Craven TE, Buse J et al (2012) Fenofibrate-associated changes in renal function and relationship to clinical outcomes among individuals with type 2 diabetes. *Diabetologia* **55**: 1641–50

JOURNAL OF DIABETES AND ITS COMPLICATIONS

HbA_{1c} variability and all-cause mortality in T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The authors aimed to determine the relationship between HbA_{1c} variability and all-cause mortality in people (n=881) with T2D followed for 2 years.

2 Median coefficient of variation ($A1c_{CV}$) data were used to categorized individuals into high- or low-HbA_{1c} variability groups. Clinical characteristics between the two groups were compared over 2 years. Subjects with a higher $A1c_{CV}$ had significantly higher all-cause mortality (P=0.002).

3 The authors concluded that $A1c_{CV}$ is an important risk factor for all-cause mortality in T2D, and that long-term survival may be influenced by maintaining good glycaemic control.

Ma WY, Li HY, Pei D et al (2012) Variability in hemoglobin A1c predicts all-cause mortality in patients with type 2 diabetes. *J Diabetes Complications* **26**: 296–300

DIABETOLOGIA

T2D and coronary angiograpy: Long-term mortality risk

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The authors investigated the association between glucose-lowering treatment and long-term mortality in people with T2D and coronary artery disease undergoing coronoary angiography.

2 Individuals (n=12 515) treated with diet, with oral therapy or insulin alone or with insulin combined with oral therapy, were followed for a mean of 4.14 years. Long-term mortality was calculated after adjusting for baseline diabetes and cardiovascular characteristics.

3 Insulin alone and insulin combined wih oral glucose-lowering treatment were both significantly associated with higher mortality rates compared with diet alone (P=0.005 and P≤0.01, respectively).

4 The authors concluded that individuals with T2D who were treated with either of these two therapies are at increased risk of mortality following coronary angiography.

Saleh N, Petursson P, Lagerqvist B et al (2012) Long-term mortality in patients with type 2 diabetes undergoing coronary angiopathy: the impact of glucose-lowering treatment. *Diabetologia* 8 May [Epub ahead of print]

"People with fenofibrate-associated creatinine increase may be more sensitive to the beneficial effects of fenofibrate whilst being at no increased risk of adverse renal or cardiovascular outcomes."