Management & prevention of type 2 diabetes

Further evidence of the risks of hypoglycaemia: An argument for prolonging use of insulin sensitisers?

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This retrospective database study (Currie et al, 2010; summarised alongside) generated two cohorts of people aged 50 and over with type 2 diabetes from the UK General Practice Research Database from November 1986 to November 2008. The first cohort was 27 965 people who had changed from oral monotherapy to combination oral therapy with metformin and a sulphonylurea. The second was 20 005 people who changed to regimens that included insulin. Mean follow-up was 4.5 years in cohort 1 and 5.2 years in cohort 2. All-cause mortality was the primary outcome. Confounding factors were identified and Cox survival models were adjusted for these factors accordingly.

The main result was that, in both groups, the 10% of people with the lowest HbA_{1c} values (<6.7% [<50 mmol/mol]) had a higher death rate than all but those in the top 10% (who had an HbA_{1c} ≥9.9% [≥85 mmol/mol). Furthermore, cardiovascular disease was more frequent in the lowest HbA_{1c} decile than in any other group.

The results overall show a U-shaped curve, with the lowest hazard ratio for death at an HbA_{1c} of 7.5% (58 mmol/mol). The hazard ratio for all-cause mortality in people given insulin-based regimens (2834 deaths) versus those given combination oral agents (2035 deaths) was 1.49. The U-shaped pattern was sufficiently similar in the two treatment cohorts to suggest that risk of mortality with respect to HbA_{1c} was independent of treatment regimen.

This study, although it supports the results of randomised controlled trials such as the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study (ACCORD Study Group et al, 2008), cannot show a causal relationship between HbA_{1c} and mortality. However, the results are consistent with the idea that premature death may be related to hypoglycaemia.

Currie et al's findings add further support to the notion that for people with type 2 diabetes treated with older insulin secretagogues or insulin itself, an HbA_{1c} of 7.5% (58 mmol/mol) corresponds to the lowest death rate, and the lowest large vessel disease event rate. It can be argued, therefore, that priority should be given to insulin sensitiser therapy to lower HbA_{1c} for as long as possible in people with type 2 diabetes because these drugs lower HbA_{1c} without risk of hypoglycaemia. When pioglitazone comes off patent within the next year, it is likely that its price will reduce to nearer that of metformin, so there will be two cheap insulin sensitiser drugs available for the treatment of the earlier stages of type 2 diabetes.

ACCORD Study Group et al (2008) Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* **358**: 2545–59.

DIABETES RESEARCH & CLINICAL PRACTICE

European T2D guidance targets largely in agreement

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1 The GUIDANCE Study Group compared the most recent nationally recognised guidelines for type 2 diabetes (T2D) from Belgium, England and Wales, France, Germany, Ireland, Italy, the Netherlands and Sweden.

2 Data on key process and outcome indicators were appraised by two independent researchers using a research evaluation instrument.

3 Guidance scores for rigour of development varied widely (e.g. 31% for The Netherlands, 95% for England and Wales).

4 Variations between guidelines were widest with respect to recommended frequency of review (e.g. lipids, blood pressure varied from 3–12 months).

5 A substantial degree of consensus for specified targets was found.

Stone MA, Wilkinson JC, Charpentier G et al (2010) Evaluation and comparison of guidelines for the management of people with type 2 diabetes from eight European countries. *Diabetes Res Clin Pract* **87**: 252–60

LANCET

High and low mean HbA_{1c} associated with increased all-cause mortality

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

1 In this retrospective cohort study, the authors assessed survival as a function of HbA_{1c} among people with type 2 diabetes. Records from the UK General Practice Research Database were the source.

2 The study population was aged 50 years or older and was divided into two cohorts. Cohort 1 (*n*=27 965) comprised those recently changed from oral monotherapy to oral combination therapy. Cohort 2 (*n*=20 005) were recently initiated on insulin following oral therapy alone.

3 The primary outcome was all-cause mortality and mean follow-up was 4.5 years in cohort 1 and 5.2 years in cohort 2.

4 For combined cohorts, median HbA_{1c} of 7.5% (58 mmol/mol; interquartile range, 7.5–7.65) had the lowest all-cause mortality hazard ratio (HR).

5 Risk of all-cause mortality and its relationship to HbA_{1c} formed a U-shaped curve: people in the lowest (median 6.4% [46 mmol/mol]) and highest (median 10.5% [91 mmol/mol]) HbA_{1c} deciles were at greatest risk of all-cause mortality.

6 Mortality HRs were highest for people in the lowest (HR, 1.52; 95% confidence interval [CI], 1.32–1.76) and highest (HR, 1.79; 95% CI, 1.56–2.06) HbA_{1c} deciles.

7 The authors concluded that the increased risk of all-cause mortality is greatest at the highest and lowest ends of the distribution of HbA_{1c} values among people with type 2 diabetes.

Currie CJ, Peters JR, Tynan A et al (2010) Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study. *Lancet* **375**: 481–9

Turn to page 100 for a debate on the implications of this paper.

BMJ

Hypos fail to account for excess mortality in intensive treatment arm of ACCORD

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1 Using retrospective epidemiological analysis, the authors aimed to determine whether a link existed between hypoglycaemia and mortality in the ACCORD trial participants.

2 Hypoglycaemia was defined as a blood glucose level <2.8 mmol/L or symptoms that required intervention.

3 Participants in the intensively treated arm who had experienced one or more hypoglycaemic episode (HE) that required medical intervention were at a significantly lower risk of death than those with the same history in the standard treatment arm (hazard ratio, 0.55; 95% confidence interval, 0.31–0.99).

4 Hypoglycaemia did not account for differences in mortality between treatment arms in the ACCORD trial.

Bonds DE, Miller ME, Bergenstal RM (2010) The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* **340**: b4909

DIABETES, OBESITY AND METABOLISM

Structured education improves biomedical and psychosocial outcomes in T2D

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

1 Type 2 diabetes (T2D) is generally managed day-to-day by the person with diabetes outside the healthcare setting. Structured self-management education (SSME) has become recognised as an integral part of the management of T2D.

2 SSME aims to give the skills and confidence to people with T2D to make informed self-care choices.

3 Significant reductions in depression, need for medication and body weight, and improvements in glycaemic control and lipid profiles have been associated with SSME, although measuring success is a challenge.

4 SSME is an integral part of modern T2D management and the body of evidence for its biomedical and psychosocial effectiveness is growing.

Jarvis J, Skinner TC, Carey ME, Davies MJ (2010) How can structured self-management patient education improve outcomes in people with type 2 diabetes? *Diabetes Obes Metab* **2**: 12–9

BMJ

Severe hypo risk a function of poor glycaemic control in ACCORD cohort

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1 A *post hoc* epidemiological analysis of ACCORD trial data was undertaken to identify determinants of severe hypoglycaemia.

2 Severe hypoglycaemia was defined as low blood glucose requiring the intervention of a third party or blood glucose level <2.8 mmol/L.

3 A 1% (11 mmol/mol) decrease in HbA_{1c} from baseline to month 4 conferred a risk reduction of 28% (95% CI, 19–37%) and 14% (95% CI, 4–23%) in the standard and intensive glycaemic control arms, respectively, for hypoglycaemia requiring medical intervention.

4 Regardless of treatment arm, the authors concluded that participants with poorer glycaemic control were at greater risk of severe hypoglycaemia.

Miller ME, Bonds DE, Gerstein HC et al (2010) The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ* **340**: b5444

BMJ

Sulphonylureas associated with increased risk of all-cause mortality

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

1 The authors of this retrospective cohort study investigated the association between prescription of oral antidiabetes drugs and risk of incident myocardial infarction (MI), congestive heart failure and all-cause mortality.

2 People (35–90 years of age) with an episode of care between 1 January 1990 and 31 December 2005 and diabetes were included (n=91 521).

3 The unit of observation was an interval of drug treatment. Primary events were first MI, congestive heart failure and all-cause mortality.

4 During follow-up (mean 7.1 years) there were 2 843 007 intervals of treatment with oral antidiabetes drugs, 3588 MIs, 6900 cases of congestive heart failure and 18 548 deaths.

5 Compared with metformin there was a significant association between treatment with a first- or second-generation sulphonylurea and excess risk of all-cause mortality that ranged from 24–61% (P<0.001).

6 Pioglitazone was significantly associated with a 31–39% lower risk of all-cause mortality (P<0.02). Compared with pioglitazone, rosiglitazone was associated with a 34–41% higher risk of all cause mortality (P<0.14 to P=0.01).

7 The findings suggest that, compared with metformin, sulphonylureas have an unfavourable risk profile. Pioglitazone was associated with reduced all-cause mortality compared with metformin and a favourable risk profile compared with rosiglitazone.

Tzo\ulaki I, Molokhia M, Curcin V et al (2009) Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ* **339**: b4731

"The findings suggest that, compared with metformin, sulphonylureas have an unfavourable risk profile."