Tighter control, poorer survival?

In this section, a panel of multidisciplinary team members give their opinions on a recently published diabetes paper. In this issue, the focus is on the results of a retrospective study of the General Practice Research Database that suggests survival is poorest for people with type 2 diabetes at both the highest and lowest HbA_{1c} levels.

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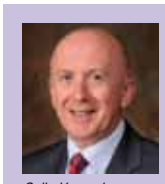
Intensive glycaemic control increases the risk of hypoglycaemia with some drugs more than with others, therefore the assessment of risks associated with different blood glucose-lowering regimens is important. In this study (Currie et al, 2009; summarised alongside) two cohorts were studied from the UK General Practice Research Database from November 1986 to November 2008. Patients whose treatment had been intensified from oral monotherapy to combination therapy and participants who had changed to regimens that included insulin were identified, with all-cause mortality being the primary outcome.

Age, sex, smoking status, cholesterol, cardiovascular risk, and general morbidity were adjusted for in the survival models. The results suggest that an HbA_{1c} of approximately 7.0–7.5% was associated with lowest all-cause mortality while an increase or decrease from this mean HbA_{1c} value was associated with heightened risk of adverse outcomes. The U-shaped pattern of risk was sufficiently similar in the two treatment cohorts to suggest that risk of mortality with respect to HbA_{1c} was independent of treatment regimen. However, the mortality risk between the two treatment cohorts differed, showing that insulin treatment was associated with an increased mortality. The insulin-treated cohort in this analysis were, however, older and had more comorbidities than those not given insulin.

This study was retrospective, with an absence of definitive causes of death coupled with possible confounding due to coding errors and lack of standardisation for HbA_{1c} measurement. The observations from this study do not mean that there is no benefit in the achievement of present glycaemic targets. Indeed, intensive glucose control early within the natural history of type 2 diabetes results in long-term all-cause and cardiovascular mortality benefits. Such observations, taken together with this study, imply that in clinical practice an individualised approach to defining an optimal HbA_{1c} target should be taken – these targets being lower early on and may require subsequent revision with the progression of the condition and development of additional comorbidities.

Marc Evans was a co-author on the article by Currie et al, 2010



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The accepted orthodoxy is that the relationship between HbA_{1c} levels in type 2 diabetes and cardiovascular (CV) risk and mortality is linear. This theory has recently been challenged by two studies that showed no significant reduction in CV outcomes with intensive glycaemic control (ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation] Collaborative Group et al, 2008; Duckworth et al, 2009), and by a further study examining such risk, that was terminated early due to increased mortality in the intensive treatment arm (ACCORD [Action to Control Cardiovascular Risk in Diabetes] Study Group et al, 2008). Outcomes from Currie et al's (2010; summarised alongside) study of a large cohort of people with type 2 diabetes from the General Practice Research Database has added further evidence to the debate surrounding HbA_{1c} targets.

Currie et al found that the 10% of people with the lowest HbA_{1c} levels (<6.7% [<50 mmol/mol]) had a higher risk of all-cause mortality than all other higher HbA_{1c} deciles, with the exception of the 10% of people with highest HbA_{1c} levels (>9.9% [>85 mmol/mol]). The adjusted hazard ratios for all-cause mortality by HbA_{1c} decile showed a U-shaped curve, irrespective of how or when HbA_{1c} was measured. The greatest risk of death and of CV event was associated with the lowest and highest HbA_{1c} values.

The Quality and Outcomes Framework (QOF) system in the UK has proved successful for the population-level management of diabetes in the primary care setting. This latest retrospective cohort study is based on data generated from the medical records of people in just such a setting.

The lowest risk for all-cause mortality was associated with HbA_{1c} levels between 7.4 and 7.7% (57 and 61 mmol/mol). This appears to suggest that the previous QOF indicator of an HbA_{1c} of 7.5% (58 mmol/mol; NHS Employers and the General Practitioners Committee, 2008), decided upon without this new information, was indeed the optimal threshold.

Presently, the QOF's lowest indicator is an HbA_{1c} of 7% (53 mmol/mol; NHS Employers and the General Practitioners Committee, 2008). It would appear that, in a large general practice population, this lower HbA_{1c} indicator is hazardous when applied across all ages groups and all regimens, particularly those including insulin and sulphonylureas.

ACCORD Study Group, Gerstein HC, Miller ME et al (2008) *N Engl J Med* **358**: 2545–59
ADVANCE Collaborative Group, Patel A, MacMahon S et al (2008) *N Engl J Med* **358**: 2560–72
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NHS Employers and the General Practitioners Committee (2008) *QOF Changes and New Indicators for 2009/10.* Available at: tinyurl.com/3okqjx (accessed 06.01.09)

Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study

Currie CJ, Peters JR, Tynan A et al (2010) *Lancet* **375**: 481–9

LANCET

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

1 Results of some recent trials have raised concerns regarding the safety of attempting to intensify antidiabetes drug regimens to reach normal blood glucose levels in people with type 2 diabetes.

2 In this retrospective cohort study, the authors assessed survival as a function of HbA_{1c} among people with type 2 diabetes. Records between November 1986 and November 2008 from the General Practice Research Database (GPRD) were the data source.

3 Inclusion criteria were age 50 years or older, type 2 diabetes with intensification of antidiabetes drug therapy and a case history of >6 months prior to intensification and >12 months following intensification.

4 Exclusion criteria were people with diabetes secondary to other complications (e.g. gestational or drug-induced diabetes).

5 The study population was divided into two cohorts. Cohort 1 (n=27 965) comprised those recently changed from oral monotherapy to oral combination therapy (a sulphonylurea plus metformin); cohort 2 (n=20 005) comprised those recently initiated on insulin following previous oral therapy alone.

6 The primary outcome was all-cause mortality, secondary outcome major cardiovascular event in those without record of cardiovascular disease prior to the index date.

7 Baseline mean HbA_{1c} was 9.0% and 10.0% (75 and 86 mmol/mol) in cohorts 1 and 2, respectively. Mean follow-up was 4.5 years (125 968 person-years) in cohort 1, and 5.2 years in cohort 2 (104 106 person-years).

8 The unadjusted mortality rate was higher in cohort 2 than in cohort 1 (27.2 and 16.2 deaths per 1000 person-years, respectively).

9 For combined cohorts, following antidiabetes therapy intensification, mortality varied by HbA_{1c} deciles, regardless of cohort.

10 A median HbA_{1c} of 7.5% (58 mmol/mol) had the lowest all-cause mortality hazard ratio (HR) and was used as the reference decile.

11 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.

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

13 The authors concluded that the increased risk of all-cause mortality at the highest and lowest ends of the distribution of HbA_{1c} values among people with type 2 diabetes. If confirmed, these findings have implications for diabetes guidelines and the need to include a minimum, not just maximum, HbA_{1c} value.

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This interesting analysis of data from the UK General Practice Research Database (summarised alongside), which demonstrates a U-shaped association between HbA_{1c} and survival in type 2 diabetes, suggests that the optimal HbA_{1c} target for glycaemic control may not lie within the non-diabetic range. Although neither the causes of death nor the frequency of exposure to hypoglycaemia could be determined in this study, a relationship may exist between therapies that promote hypoglycaemia, namely insulin and sulphonylureas, and increased risk of mortality. While the UKPDS (UK Prospective Diabetes Study) showed that strict glycaemic control limits the long-term risks of vascular disease (Stratton et al, 2000), this aspiration would appear to be rendered superfluous by the revelation that it may also be associated with a greater risk of death.

These observations are consistent with the disconcerting findings of the ACCORD Group et al (2008) and the VADT (Veterans Affairs Diabetes Trial; Duckworth et al, 2009) – large trials that examined whether strict glycaemic control could prevent major cardiovascular (CV) events and premature death. The contrary findings have made physicians think twice about attempting aggressive lowering of HbA_{1c} – at least in people with concurrent coronary heart disease. While the causes of the fatal CV events in these trials could not be determined with veracity, hypoglycaemia has been strongly implicated as a precipitant.

Hypoglycaemia is hazardous. It can induce cardiac arrhythmias, myocardial ischaemia and cerebrovascular events (Wright and Frier, 2008; Graveling and Frier, 2010). This association was absent in the findings of the ADVANCE Collaborative Group (2008), where the use of insulin and the frequency of severe hypoglycaemia were much lower than in the ACCORD and VADT cohorts.

It is now apparent that hypoglycaemia should be avoided in people with macrovascular disease. In addition, studies in intensive care settings of the glycaemic management of people with diabetes have consistently shown a U-shaped curve relating low blood glucose with higher mortality (e.g. Pinto et al, 2008; Ishihara et al, 2009). The present study adds to the mounting evidence that challenges current international guidelines for glycaemic control and is forcing reconsideration of what targets are appropriate in type 2 diabetes.

ACCORD Group et al (2008) *N Engl J Med* **358**: 2545–59
ADVANCE Collaborative Group (2008) *N Engl J Med* **358**: 2560–72
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Stratton IM, Adler AI, Neil HA et al (2000) *BMJ* **321**: 405–12
Wright RJ, Frier BM (2008) *Diabetes Metab Res Rev* **24**: 353–63

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Currie et al's (2010; summarised alongside) careful analysis of retrospective general practice data adds to concerns about possible harms associated with tight glycaemic control. Hopefully, inappropriate extrapolation of these results, and those from recent trials (ACCORD Study Group et al, 2008; ADVANCE Collaborative Group, 2008; Holman et al, 2008; Duckworth et al, 2009), plus limited consideration of context, will not threaten the delivery of effective preventive care.

Currie et al's findings apply to those whose treatment was increased from one drug, and not to behavioural approaches or initiation of first-line treatment. Furthermore, data used dated back to 1986 – at which time diabetes care was rather different from today. For example, baseline HbA_{1c} values (median >9.0% [>75 mmol/mol]) were much higher than the levels achieved more recently in primary care (in 2005, 85% of people with diabetes had values <9%; Graffy and Griffin, 2008).

Currie et al report an observational study, so results may be explained by confounding factors other than treatment. In contrast, meta-analyses of trial data, which are much less likely to be affected by confounding and bias, demonstrate reductions in cardiovascular (CV) risk and no increase in mortality associated with intensive treatment of hyperglycaemia (Ray et al, 2009; Turnbull et al, 2009). Follow-up was short (4 years) in Currie et al's study. It seems that harms associated with tight glycaemic control become apparent in the short term but it can take several years to demonstrate the benefits (ACCORD Study Group et al, 2008; Holman et al, 2008).

Blood glucose is an independent CV risk factor, albeit not a very strong one; people with higher blood glucose levels have a higher risk of CV complications (21% higher risk of diabetes-related death for each 1% [11 mmol/mol] increase in HbA_{1c}; Stratton et al, 2000). However, available antidiabetes drugs certainly have limitations and only metformin has been shown to reduce both CV events and death among people with type 2 diabetes (Holman et al, 2008).

Adding treatment to achieve rapid, large reductions in HbA_{1c} towards 6% (42 mmol/mol) among people with long-standing poor glycaemic control should be undertaken with caution. Nevertheless, good management should continue to include intensive treatment of multiple risk factors – which can reduce CV risk and mortality by half (Gaede et al, 2008) – and negotiation of treatment targets between the person with diabetes and their healthcare professional.

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