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Since publication of the troubling results from the ACCORD trial[1] in mid-2008, which showed that intensive treatment of type 2 diabetes was associated with a higher all-cause mortality than was conventional therapy, an explanation has been sought. The goal for people intensively treated was a glycated haemoglobin (HbA_{1c}) of less than 6·0%. At the end of 3·5 years, when the trial was prematurely terminated, the HbA_{1c} achieved was 6·4% in the intensively treated and 7·5% in the conventionally treated groups; HbA_{1c} was 8·1% at inclusion. The most plausible explanation for these results is hypoglycaemia: the treatment target was probably too low, or glucose lowering was too rapid, or the combinations of treatments led to hypoglycaemia.

By contrast, researchers from the ADVANCE[2] and VADT[3] studies reported no increase in mortality in intensively treated patients. Meta-analyses of the three trials, and of the UKPDS and the PROactive trials,[4–6] had sufficient power to conclude that although intensive treatment was associated with a lowered rate of major cardiovascular events and myocardial infarctions, it had no effect on mortality. Results were homogeneous between trials, but ACCORD[1] was the only one that showed a significant increase in mortality. Findings from the UKPDS,[7] which included younger (median age 54 years), newly diagnosed patients, showed a substantially lowered all-cause mortality and rate of myocardial infarction in the 10-year post-trial follow-up for those originally allocated to intensive therapy. This outcome suggests a legacy of early intensive treatment. In all studies,[5] hypoglycaemia was more frequent in the intensively treated than in the conventionally treated group.

In *The Lancet* today, some light is thrown on this issue by Craig Currie and colleagues,[8] with data from the large and statistically powerful General Practice Research Database, which has gathered data electronically from general practitioners in the UK. The main result in this study of 48 000 patients with type 2 diabetes (cohort 1 changed from monotherapy to combination oral therapy with metformin and a sulphonylurea; cohort 2 changed to insulin treatment) is that the 10% of patients with lowest HbA_{1c} values (<6·7%) had a higher death rate than all but those in the top 10%, who had an HbA_{1c} of 9·9% or higher. Furthermore, cardiovascular disease was more frequent in this low HbA_{1c} group than in any other decile. Similar results were reported in the two cohorts analysed with different definitions of how HbA_{1c} was used in statistical analyses and after adjustment for the main covariates associated with mortality. The hypothesis that premature death might be related to hypoglycaemia is also supported by the finding that for those with an HbA_{1c} of less than 6·7%, the insulin treated group had a higher hazard ratio (HR) for mortality (1·79, 95% CI 1·45–2·22) than did those not treated with insulin (HR 1·30, 1·07–1·58), compared with the reference decile 4 in which HbA_{1c} was 7·4–7·7%. Furthermore, in the insulin treated, all three lower-decile groups had higher mortality than did the reference decile group, by contrast with the orally treated group, in which only the first-decile group had higher mortality. A previous study[9] showed that in patients with type 2 diabetes, insulin therapy was more closely related to hypoglycaemia (odds ratio [OR] 3·44, 2·07–5·73) than sulphonylurea therapy (OR 1·54, 0·95–2·50), and low HbA_{1c} levels were also associated with any hypoglycaemia, with an OR per 1% decrease in HbA_{1c} of 1·15 (1·04–1·29).

Causes of death were not given in Currie and colleagues' report—was sudden death a more common cause in those with low HbA_{1c}? No information is provided about the actual insulin or oral doses, or drugs used for treatment. A study[10] that used the same database showed that first-generation sulphonylurea monotherapy was associated with higher mortality (HR 1·37, 1·11–1·71) than was second-generation sulphonylurea monotherapy (HR 1·24, 1·14–1·35) compared with metformin. Another study from the Saskatchewan Health administrative

databases[11] implicated insulin exposure with increased mortality, with a dose-response relation in patients with type 2 diabetes.

Although today's study does lend support to results of earlier studies, an epidemiological study cannot show a causal relation, and such an observational database does not provide the detailed information that is available in a randomised clinical trial, such as the frequency of hypoglycaemia. However, this study has the advantage of dealing with observations in the real world: the choice of the treating physician in prescribing specific drugs might well depend on the severity of the patient's illness and probable lifespan. Ideally, only randomised clinical trials of intensive treatment with continuous glycaemic monitoring to detect all hypoglycaemia in all groups of patients (especially in those who will die) would resolve this issue. Because this option is not feasible, careful monitoring of all hypoglycaemic events with stringent definitions, which are still under discussion,[12] should be included in the trial design to assess the effect of hypoglycaemia on death and cardiovascular events. Key elements in the use of drugs that can provoke hypoglycaemia are the education of patients to recognise hypoglycaemia and systematic reporting of all hypoglycaemia.[13]

In patients with type 2 diabetes, when using insulin secretagogues or insulin itself, today's study does provide a rationale for an HbA_{1c} threshold of 7·5%, corresponding to the lowest death rate and lowest event rate for large-vessel disease. Priority should be given to insulin sensitisers for as long as possible in patients with type 2 diabetes, because these drugs allow a low HbA_{1c} to be targeted without any risk of hypoglycaemia. More research is needed to establish HbA_{1c} thresholds and the combination of drugs to be recommended for intensive treatment, with perhaps differing recommendations according to the patient—intensive treatment seems to be more beneficial for cardiovascular outcomes for those who are younger than 60 years, with a short duration of diabetes, and absence of microvascular and macrovascular disease.[5]

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