Survival in people with type 2 diabetes as a function of HbA1c

Since publication of the troubling results from the ACCORD trial 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 (HbA1c) of less than 6·0%. At the end of 3·5 years, the HbA1c achieved was 6·4% in the intensively treated and 7·5% in the conventionally treated groups; HbA1c was probably too low, or glucose lowering was too rapid, or the combinations of treatments led to hypoglycaemia.

By contrast, researchers from the ADVANCE2 and VADT3 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 ACCORD3 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 colleagues8 with data from the large 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), the main result is that the 10% of patients with lowest HbA1c values (<6·7%) had a higher death rate than all but those in the top 10%, who had an HbA1c of 9·9% or higher. Furthermore, cardiovascular disease was more frequent in this low HbA1c group than in any other decile. Similar results were reported in the two cohorts analysed with different definitions of hypoglycaemia.

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My research laboratory has received research grants from several ventilator companies (Maquet, Dräger, Philips Respironics, General Electric), but has no relationship to disclose for the use of sedation in intensive care.

of how HbA1c 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 HbA1c 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 HbA1c was 7.4–7.7%. Furthermore, in the insulin treated group, 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 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 HbA1c levels were also associated with any hypoglycaemia, with an OR per 1% decrease in HbA1c of 1.15 (1.04–1.29).

Causes of death were not given in today’s report—was sudden death a more common cause in those with low HbA1c? No information is provided about the actual insulin or oral doses, or drugs used for treatment. A study 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 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, 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.

In patients with type 2 diabetes, when using insulin secretagogues or insulin itself, today’s study does provide a rationale for an HbA1c threshold of 7.5%, corresponding to the lowest death rate and lowest event rate for large-vessel disease. Priority should be given to insulin sensitiser for as long as possible in patients with type 2 diabetes, because these drugs allow a low HbA1c to be targeted without any risk of hypoglycaemia. More research is needed to establish HbA1c 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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Safer childbirth: avoiding medical interventions for non-medical reasons

3 years ago, The Lancet published the 2005 WHO global survey on maternal and perinatal health,¹ which documented the high rates of caesarean sections in Latin America and the association with severe maternal and perinatal morbidity and mortality. That year, a new warning was issued about the dangers of unnecessary caesarean section.² However, controversy about the ideal rate of caesarean section³ and the place of maternal choice⁴ has been continuing for so long that many obstetricians have become accustomed to the practice of medical interventions for non-medical reasons. I (Y-SC) was once dumbfounded to overhear a remark at a professional workshop that “the best birth plan any woman can have is to ask for an elective caesarean section”. No doubt that remark was made facetiously, but the inconvenient truth is that physicians are some of the main advocates of this intervention to their patients, themselves, and their relatives.⁵

In The Lancet today, this situation is highlighted by Pisake Lumbiganon and colleagues in the 2007–08 WHO global survey,⁶ which provides a careful examination of childbirth practices in nine Asian countries. Acknowledging the difficulties of separating the intrinsic risk of procedures from the underlying medical indications, these authors classified caesarean sections into those with and without indications, and vaginal deliveries into spontaneous and operative deliveries. And the results are surprising and chilling.

Although the overall rate of caesarean section was lower than that in Latin America (27% vs 33%), regional practice in the nine Asian countries differed substantially: rates in four countries exceeded 30%, whereas rates in the remaining five were less than 21%. In the country with the highest rate (China, 46.2%), a quarter of caesarean sections were done without medical indications—a rate far higher than that in the other countries surveyed. The reasons for this astonishing difference in practice were...

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