HbA_{1c} and survival in type 2 diabetes

When treating diabetes, it is now assumed that the lower the HbA_{1c}, the better the outcome for the individual – to minimise the risk of long-term vascular complications. Robust evidence for the beneficial effects of strict glycaemic control was provided by the DCCT (Diabetes Control and Complications Trial; DCCT Research Group, 1993), and the UKPDS (UK Prospective Diabetes Study; UKPDS Group, 1998). In the UK, to encourage GPs to strive for stricter glycaemic control of people with diabetes, the threshold for the lowest HbA_{1c} indicator for QOF has been lowered from 7.5% to 7.0% (58 to 53 mmol/mol).

These therapeutic aspirations are unlikely to harm people with type 2 diabetes who are managed with diet or oral antidiabetes drugs (OADs) that seldom cause hypoglycaemia. However, treatment with insulin or sulphonylureas is a different matter. The merit of pursuing a policy of ever-lower HbA_{1c} concentrations for everyone with type 2 diabetes has been challenged by the outcome of large clinical studies (ACCORD [Action to Control Cardiovascular Risk in Diabetes] Study Group et al, 2009; Duckworth et al, 2009), which have demonstrated that the use of intensive therapy to attain very strict glycaemic control is potentially hazardous. An increased risk of serious cardiovascular (CV) events and excess mortality was observed in people with type 2 diabetes with established CV disease or who had several vascular risk factors.

Severe hypoglycaemia can cause potentially serious morbidity and sudden death (Wright and Frier, 2008), and although it was not possible to prove that hypoglycaemia had caused cardiac arrhythmias or myocardial ischaemia in the ACCORD study, it is clear that strict glycaemic control is not appropriate for every person with type 2 diabetes.

A more recent study using the large UK General Practice Research Database revealed an unfavourable risk profile of sulphonylureas compared with metformin, which could suggest a greater risk of hypoglycaemia associated with these drugs (Tzoulaki et al, 2009).

Another study using the same research database has now added to the controversy surrounding HbA_{1c} targets. Currie et al (2010) examined the relationship between HbA_{1c} and survival using data collected for more than 20 years from 48 000 people with type 2 diabetes. One cohort (*n*=27 965) had been changed from OAD monotherapy to a combination of OAD medications, while the other cohort (*n*=20 005) had commenced regimens that included insulin – consistent with the escalation in therapy that is associated with the progressive severity of type 2 diabetes. The primary outcome measure of all-cause mortality was examined for each decile of HbA_{1c} in both cohorts.

The 10% of people who had the lowest HbA_{1c} levels (<6.7%; <50 mmol/mol) had a higher mortality than all other deciles with higher HbA_{1c} levels, with the exception of the 10% with the highest HbA_{1c} levels of ≥9.9% (≥85 mmol/mol). The adjusted hazard ratios for all-cause mortality by HbA_{1c} deciles showed a U-shaped curve, irrespective of how or when HbA_{1c} was measured. The greatest risk of death and of cardiac events was associated with the lowest and highest HbA_{1c} values – although the causes of death were not known, nor could the frequency of hypoglycaemia be determined in this retrospective analysis. Interestingly, the lowest risk was associated with HbA_{1c} levels in the decile of 7.4–7.7% (57–61 mmol/mol). Thus it would appear that the choice of the original QOF target for the lowest HbA_{1c} level of 7.5% (58 mmol/mol), which was made without this new information, was indeed the optimal threshold.

So what should be the lowest HbA_{1c} target in people with type 2 diabetes? This must be tailored to the age of the individual and should address their existing comorbidities and the treatment to be used. Indiscriminate application of intensive glucose-lowering therapy that could provoke dangerous hypoglycaemia in frail older people with type 2 diabetes, or in those with overt CV disease, should be avoided. In the light of this emerging evidence, a blanket approach that aims for progressively lower HbA_{1c} levels (as currently stipulated by QOF) could raise ethical concerns, and a risk assessment of the individual is essential before aiming to lower HbA_{1c} below 7%. ■

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