Management & prevention of type 2 diabetes

Tightening glycaemic control: A marathon and not a sprint?

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These important data from the post-trial monitoring phase of the UKPDS (UK Prospective Diabetes Study) underline an essential message for clinical practice and for the configuration of diabetes services. Optimal management of glycaemic control in the treatment of diabetes is an "endurance event", in that people with diabetes and the healthcare professionals helping them must be clear from the outset they are playing the long game. The micro- and macrovascular benefits of improved glycaemic control emerge more clearly with longer-term follow-up, become increasingly apparent with longer disease duration, and translate to real, relevant, clinically important advantages for people with diabetes. The message seems to be: invest today (in terms of improved glycaemic control) and you will reap the reward tomorrow (in terms of improved health and a reduced risk of complications).

Irrespective of the primary treatment allocation in the UKPDS (metformin or sulphonylurea and insulin), those in the intensively treated groups had a reduced risk of diabetes-related microvascular endpoints, lower myocardial infarction rates, and a reduced risk of death from any cause. These advantages became increasingly apparent with increasing time since primary randomisation. The advantages of early tight control persisted, despite the fact that the HbA_{1c} difference between the conventional and intensively treated people disappeared within 1 year of the end of the study.

Collectively, these findings raise the possibility that the end (improved glycaemic control) is more important than the means (how this is achieved) and more significantly introduce the concept of "glycaemic memory". Simply stated, what happens in the diabetes clinic today, and how that translates into the daily lived experience of diabetes in terms of ambient glycaemia for the individual, will directly influence his or her expression of vascular disease in 10–20 years' time.

This message contrasts with the data from ACCORD (Action to Control Cardiovascular Risk in Diabetes), where people 8–12 years older with longer-duration diabetes (8–10 years) and a higher prevalence of established vascular complications had a significantly increased mortality rate when they underwent rapid glycaemic intensification (the target HbA_{1c} level in the intensively treated group was <6.0%, compared with 7.0–7.9% in the standard therapy arm; ACCORD Study Group, 2008). In contrast to the real benefits that emerged over the 20 years of the UKPDS, real harm was done over 3.5 years in the ACCORD study. While the reason for the excess mortality rate is not clear, unrecognised hypoglycaemia in a population with established vasculopathy seems the likely culprit, and, certainly, rapid intensification of glycaemic control in this group seems a step too far, too late.

The findings from the UKPDS regarding follow-up of intensive glucose lowering also contrast with post-trial monitoring data from the antihypertensive therapy arm (Holman et al, 2008). The latter were reported in an article in the same issue of the *New England Journal of Medicine*, and showed that the benefits of intensive antihypertensive therapy are quick to appear but also quick to disappear.

The sustained legacy of an intensive glycaemic control strategy emphasises that the benefits of optimal glycaemic control emerge for people over the marathon of a life with diabetes.

Holman RR, Paul SK, Bethel MA et al (2008) Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med* **359**: 1565–76

The Action to Control Cardiovascular Risk in Diabetes Study Group (2008) Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* **358**: 2545–59

NEW ENGLAND JOURNAL OF MEDICINE

Emergent benefits of tight glycaemic control

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

1 The current investigators carried out post-trial monitoring to determine whether the microvascular risk reductions evident with intensive glucose-lowering therapy in the UK Prospective Diabetes Study (UKPDS) persisted. In addition, they aimed to determine whether the original intervention had any long-term macrovascular benefit.

2 Of the original UKPDS population, 3277 people with type 2 diabetes were invited to annual post-trial monitoring clinics for the first 5 years after the end of the study. In years 6–10, participants were assessed by questionnaire.

3 After 1 year, the original between treatment-group differences that existed in HbA_{1c} levels were lost. Compared with those in the conventional therapy (diet alone) group, those who received sulphonylurea or insulin therapy retained a lower risk of microvascular complications and any diabetes-related endpoint after 10 years.

4 Interestingly, relative risk reductions for all-cause mortality and myocardial infarction also emerged in these intensively treated people (13% and 15%, respectively; $P=0.007$ and $P=0.01$).

5 In those originally treated with metformin, relative risk reductions for all-cause mortality, myocardial infarction and any diabetes endpoint remained statistically significant (27%, 33% and 21%, respectively; $P=0.002$, $P=0.005$ and $P=0.01$).

Holman RR, Paul SK, Bethel MA et al (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* **359**: 1577–89.

DIABETES CARE

Retinopathy risk dependent on age of type 2 diabetes onset

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

1 The current study was undertaken to assess the hypothesis that risk of retinopathy is dependent on the age of type 2 diabetes onset – independently of disease duration and glycaemic control.

2 The investigators found that younger age of onset (<45 years, and 45–55 years, as compared with >55 years) was indeed associated with an increased susceptibility to retinopathy.

Wong J, Molyneaux L, Constantino M et al (2008) Timing is everything: age of onset influences long-term retinopathy risk in type 2 diabetes, independent of traditional risk factors. *Diabetes Care* **31**: 1985–90

DIABETES CARE

Hyperglycaemia in utero and onset of type 2 diabetes

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

1 The present investigators examined a cohort of young people diagnosed with diabetes between 2001 and 2005, each of whom had a parent with diabetes.

2 Type 2 diabetes, but not type 1 diabetes, was diagnosed earlier (by 1.68 years) in those people who had been exposed to maternal diabetes in utero compared with those whose mothers had diabetes diagnosed later.

Pettitt DJ, Lawrence JM, Beyer J et al (2008) Association between maternal diabetes in utero and age at offspring's diagnosis of type 2 diabetes. *Diabetes Care* **31**: 2126–30

DIABETES CARE

New 5-year CVD risk equation

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

1 The current authors present a prediction equation for estimating absolute 5-year risk of primary fatal or non-fatal cardiovascular disease (CVD) in people with type 2 diabetes.

2 The equation is based upon data from over 11 500 people from the Swedish National Diabetes Register, and incorporates HbA_{1c} level and eight non-laboratory clinical predictors (e.g. smoking status and age of diabetes onset).

Cederholm J, Eeg-Olofsson K, Eliasson B et al (2008) Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. *Diabetes Care* **31**: 2038–43

"Type 2 diabetes, but not type 1 diabetes, was diagnosed earlier in those people who had been exposed to maternal diabetes in utero compared with those whose mothers had diabetes diagnosed later."