Diabetes journals

Setting the right targets for optimal glycaemic control in people with type 2 diabetes

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There is conflicting evidence regarding appropriate glycaemic indicators for people with type 2 diabetes. A number of large-scale clinical trials aiming for near-normal HbA_{1c} have failed to demonstrate significant benefits on major cardiovascular (CV) events or death (UK Prospective Diabetes Study [UKPDS] Group, 1998a; 1998b; Abraira et al, 2003; Charbonnel et al, 2004; Dormandy et al, 2005; Action to Control Cardiovascular Risk in Diabetes Study Group et al, 2008; ADVANCE Collaborative Group et al, 2008; Wilcox et al, 2008; Duckworth et al, 2009), although a meta-analysis of these trials has shown modest benefits for cardiovascular events, but not mortality (Ray et al, 2009). Furthermore, an epidemiological analysis of the relationship between glucose control and outcome in people with type 2 diabetes has implied a potential association between intensive glycaemic control and an increase in mortality, suggesting a potential threshold effect for optimal glycaemic control (Currie et al, 2012).

Zoungas et al (2012; summarised alongside) investigated the relationship between HbA_{1c} and the risk of vascular complications and death in people with type 2 diabetes in the Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Glycaemic exposure was defined as the mean value of HbA_{1c} measurements during follow-up and prior to the first event. Adjusted risks for each HbA_{1c} decile were estimated using Cox models. Possible differences in the association between HbA_{1c} and risk at different HbA_{1c} levels were explored using linear spline models.

The risk of CV complications and death were strongly associated with glycaemic exposure and evidence of HbA_{1c} "thresholds" – at which the lowest CV event rates were observed – was noted. Above these thresholds participants experienced a significantly higher risk of macrovascular and microvascular events and death in a log-linear relationship. Below them, there was no significant relationship between mean HbA_{1c} level and risks and, in particular, no evidence of harm. For macrovascular events and death the apparent threshold HbA_{1c} level was 7.0% (53 mmol/mol), and for microvascular events 6.5% (48 mmol/mol).

> ***"The risk of cardiovascular complications and death were strongly associated with glycaemic exposure and evidence of HbA_{1c} "thresholds" ... was observed; ... for macrovascular events and death the apparent threshold HbA_{1c} level was 7.0% (53 mmol/mol), and for microvascular events 6.5% (48 mmol/mol)."***

These data demonstrate that achieving HbA_{1c} levels of 7.0% and 6.5%, respectively, may be rewarded by outcome benefits from the perspective of both macrovascular and microvascular events.

Abraira C, Duckworth W, McCarren M et al (2003) *J Diabetes Complications* **17**: 314–22

Action to Control Cardiovascular Risk in Diabetes 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

Charbonnel B, Dormandy J, Erdmann E et al (2004) *Diabetes Care* **27**: 1647–53

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

Dormandy JA, Charbonnel B, Eckland DJ et al (2005) *Lancet* **366**: 1279–89

Duckworth W, Abraira C, Moritz T et al (2009) *N Engl J Med* **360**: 129–39

Ray KK, Seshasai SR, Wijesuriya S et al (2009) *Lancet* **373**: 1765–72

UK Prospective Diabetes Study (UKPDS) Group (1998a) *Lancet* **352**: 837–53

UK Prospective Diabetes Study (UKPDS) Group (1998b) *Lancet* **352**: 854–65

Wilcox R, Kupfer S, Erdmann E (2008) *Am Heart J* **155**: 712–17

DIABETOLOGIA

HbA_{1c} level threshold for CV outcome prevention in T2D

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

1 Given the conflicting evidence in the literature regarding appropriate glycaemic targets for people with type 2 diabetes, the authors investigated the relationship between HbA_{1c} and the risk of cardiovascular (CV) complications and death in people with T2D.

2 Some 11 140 participants were randomised to intensive or standard glucose control in the ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial.

3 Within the range of HbA_{1c} studied (5.5–10.5% [37–91 mmol/mol]), there was evidence of "thresholds", such that below HbA_{1c} levels of 7.0% (53 mmol/mol) for macrovascular events and death, and 6.5% (48 mmol/mol) for microvascular events, there was no significant change in risk (all $P>0.8$). Above these thresholds, the risk increased significantly: every 1% higher HbA_{1c} level was associated with a 38% higher risk of a macrovascular event, a 40% higher risk of a microvascular event and a 38% higher risk of death (all $P<0.0001$).

4 The authors concluded that in people with T2D, HbA_{1c} levels are associated with lower risks of macrovascular events and death down to a threshold of 7.0% and microvascular events down to a threshold of 6.5%; they found no evidence of lower risks below these levels, but neither was there clear evidence of harm.

Zoungas S, Chalmers J, Ninomiya T et al (2012) Association of HbA1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. *Diabetologia* **55**: 636–43.

DIABETES CARE

Single tool for assessing cardiometabolic risk

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

1 People at high risk of chronic cardiometabolic diseases (i.e. cardiovascular disease [CVD], T2D, chronic kidney disease [CKD]) share many risk factors and would benefit from early intervention. The aim of the study was to develop a non-laboratory-based risk-assessment tool for identification of people at high cardiometabolic disease risk.

2 Data from three population-based cohorts from different regions of the Netherlands were merged. Participants were 2840 men and 3940 women, white, aged 28–85 years and free from CVD, T2D and CKD diagnosis at baseline. The primary outcome was developing cardiometabolic disease during 7 years of follow-up.

3 Age, BMI, waist circumference, antihypertensive treatment, smoking, family history of myocardial infarction or stroke and family history of diabetes were significant predictors, whereas former smoking, history of gestational diabetes, and use of lipid-lowering medication were not.

4 Acceptable calibration (Hosmer and Lemeshow statistics, $P>0.05$) and discrimination (area under the receiver operating characteristic curve, 0.82 [95% confidence interval [CI], 0.81–0.83] for women and 0.80 [95% CI, 0.78–0.82] for men) was shown.

5 The authors concluded that the tool developed was robust enough to be used as a risk stratification tool to identify people at high risk of future cardiometabolic diseases and can be used as part of referral criteria.

Alssema M, Newson RS, Bakker SJ et al (2012) One risk assessment tool for cardiovascular disease, type 2 diabetes, and chronic kidney disease. *Diabetes Care* **35**: 741–8

DIABETES CARE

Predicting cardiovascular mortality for T2D

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

1 To evaluate the predictive role of increased corrected QT (QTc) and QT interval dispersion (QTd) on all-cause and cardiovascular mortality in a large, unselected T2D population, the authors undertook the prospective study described here.

2 Outcomes were both all-cause and cardiovascular mortality assessed at 15 years after baseline examination.

3 Some 1357 people with T2D were recruited; all baseline QTc (>0.44 s) and QTd (>0.08 s) intervals were abnormally prolonged.

4 Cardiovascular mortality was found to be significantly increased in participants with prolonged QTd (hazard ratio, 1.26; 95% confidence interval, 1.02–1.55) and was only slightly reduced after multiple adjustments; however, prolonged QTc did not increase the HR for all-cause or cardiovascular mortality.

5 The authors concluded that increased QTd is a predictor of long-term cardiovascular mortality in people with T2D.

Giunti S, Gruden G, Fornengo P et al (2012) Increased QT interval dispersion predicts 15-year cardiovascular mortality in type 2 diabetic subjects. *Diabetes Care* **35**: 581–3

DIABETIC MEDICINE

Specific SU–met combinations not linked to increased mortality risk

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

1 To assess the risk of overall mortality in people (n=7320) with T2D treated with different combinations of sulphonylureas (SU) and metformin (met) a retrospective cohort study was conducted.

2 No significant difference in overall mortality risk was observed among the different combinations of SU and met (all hazard ratios ≥1.03).

3 The authors concluded that no increased mortality risk could be found between the different combinations of SU and met, suggesting that overall mortality is not substantially influenced by the choice of SU.

Pantalone KM, Kattan MW, Yu C et al (2012) The risk of overall mortality in patients with type 2 diabetes receiving different combinations of sulfonylureas and metformin: a retrospective analysis. *Diabet Med* Jan 16 [Epub ahead of print]

DIABETOLOGIA

Low dietary potassium linked to T2D risk

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

1 Potassium intake was measured by three 24-hour urinary potassium collections at the 5-year study visit.

2 Of the 1066 participants with urinary potassium measurements, 99 (9.3%) developed diabetes over 15 years of follow-up; participants in the lowest urinary potassium quintile were more than twice as likely to develop diabetes as their counterparts in the highest quintile (hazard ratio, 2.45; 95% confidence interval, 1.08–5.59).

3 Black Americans were found to have a significantly increased risk of diabetes with lower potassium intake, which was not found in whites.

4 The authors concluded that low dietary potassium is associated with increased risk of incident diabetes in African Americans.

Chatterjee R, Colangelo LA, Yeh HC et al (2012) Potassium intake and risk of incident type 2 diabetes mellitus: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Diabetologia* **55**: 1295–303

> *"The tool developed was robust enough to be used as a risk stratification tool to identify people at high risk of future cardiometabolic diseases and could be used as part of referral criteria."*