Major journals

To reduce HbA_{1c} or not to reduce HbA_{1c}, that is the question.

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If Hamlet had been a diabetologist, he would have had to wax lyrical over whether to intensively improve glycaemic control or not. In 2014, this is our current dilemma in the management of people with type 2 diabetes. Data from the UKPDS (UK Prospective Diabetes Study) clearly showed that intensively treated patients had significantly less microvascular disease than those who received standard treatment, with a trend towards a reduction in ischaemic heart disease that was not significant in the primary analyses (*P*=0.052; Stratton et al, 2000). However, the two treatment groups only had a modest difference in HbA_{1c} of 10 mmol/mol (0.9%), and the intensive treatment group was only treated to an HbA_{1c} of 53 mmol/mol (7.0%). Later, the VADT (Veterans Affairs Diabetes Trial) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) study indicated that intensively treated patients had a significant increase in cardiovascular mortality (Duckworth et al, 2009; Riddle et al, 2010).

In their article (summarised alongside), Gerstein et al specifically report on the ischaemic heart disease outcomes of ACCORD over the 3.7 years of the study. The rate of myocardial infarction (MI) was significantly reduced by 20% in the intensive therapy group (who achieved a final HbA_{1c} of 54 mmol/mol [7.1%]) in comparison with the standard treatment group (final HbA_{1c}, 60 mmol/mol [7.6%]). The incidence of the combined cardiovascular outcome of MI, coronary revascularisation and unstable angina was significantly reduced by 11%, and the rate of coronary revascularisation by 16%.

The exact cause of the increased cardiovascular mortality seen in the ACCORD study remains a mystery. Indeed, 80% of the deaths were judged as not being due to fatal MI (ACCORD Study Group, 2011). Ischaemic heart disease may, therefore, not be related to the increase in mortality rate, and other reasons may apply. Patients whose HbA_{1c} did not reduce despite intensive treatment had the highest risk of death. Whether this was due to hypoglycaemia, arrhythmias or an effect of polypharmacy remains unknown.

The question remains: to reduce HbA_{1c} or not to reduce HbA_{1c}? More evidence and more meta-analyses will accrue. For now, we should diligently seek to individualise HbA_{1c} targets for our patients based on their comorbidities, duration of diabetes, individual choices and whether the targets can indeed be achieved without excessive polypharmacy. This article highlights the fact that much remains unknown when it comes to improving glycaemic control, but that there are also very real prospects of benefit with regard to ischaemic heart disease. ■

ACCORD Study Group (2011) Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* **364**: 818–28

Duckworth W, Abraira C, Moritz T et al (2009) Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* **360**: 129–39

Riddle MC, Ambrosius WT, Brillon DJ et al (2010) Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* **33**: 983–90

Stratton IM, Adler AI, Neil HA et al (2000) Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* **321**: 405–12

Lancet

ACCORD study: Intensive glycaemic control reduces risk of ischaemic heart disease in T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 The authors report the effects of intensive glucose-lowering therapy on indices of ischaemic heart disease in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study.

2 A total of 10 251 people with T2D were randomised to either intensive (HbA_{1c} target, <42 mmol/mol [6.0%]) or standard therapy (HbA_{1c} target, 53–63 mmol/mol [7.0–7.9%]).

3 Participants were followed up for a mean of 3.7 years initially, then for a further 1.2 years following discontinuation of the intensive therapy owing to increased cardiovascular mortality.

4 Overall, 1263 ischaemic events occurred during the active period and 1619 during the whole follow-up. During active treatment, the risk of myocardial infarction (MI) was significantly lower in the intensive treatment group (hazard ratio, 0.80).

5 Intensive therapy resulted in significant reductions in the 5-year incidence of ischaemic heart disease (13%), any MI (16%), non-fatal MI (19%), coronary revascularisation (16%) and unstable angina (19%).

6 These results, coupled with the fact that >80% of deaths were deemed not to be a result of MI, suggest that factors other than MI are to blame for the increased mortality rate in the intensive treatment group.

7 The authors conclude that high HbA_{1c} is a modifiable risk factor for ischaemic heart disease in people with T2D.

Gerstein HC, Miller ME, Ismail-Beigi F et al (2014) Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. *Lancet* 31 Jul [Epub ahead of print]

PLoS One

Effect of glycaemic control on achieving blood pressure goals

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 Tight control of HbA_{1c} has been shown to reduce the incidence of microvascular disease in people with T2D; however, its effects on the risk of hypertension are less well known.

2 In this large, cross-sectional study of 29 442 Chinese people with T2D, the authors asesssed whether an HbA_{1c} of 6.5–6.9% (48–52 mmol/mol) or higher was associated with increased risk of poor blood pressure (BP) control (defined as failing to meet the American Diabetes Association [ADA] target BP of <140/80 mmHg).

3 Of the total cohort, 18 350 people with T2D but no known hypertension (BP ≥140/90 mmHg) were evaluated. Of these, 12 129 (66.1%) failed to meet the ADA target.

4 After adjustment for age, gender, BMI and diabetes duration, compared with those who achieved an HbA_{1c} of <6.0% (42 mmol/mol), participants with an HbA_{1c} of 6.5%–6.9%, 7.0%–7.9% and ≥8.0% were more likely to fail to meet the ADA BP target (odds ratios, 1.22, 1.37 and 1.22, respectively).

5 These findings were replicated after reinclusion of 11 902 people with diagnosed hypertension for a sensitivity analysis.

6 The results confirm that suboptimal glycaemic control, even when achieving an HbA_{1c} of <7%, affects the likelihood of achieving ADA targets for BP. The authors propose that this is because of the excitatory effect of hyperglycaemia on the renin–angiotensin system, which plays a role in hypertension, dyslipidemia and glucose intolerance.

Ji L, Zhi X, Lu J et al (2014) Hyperglycemia and blood pressure treatment goal: a cross sectional survey of 18 350 patients with type 2 diabetes in 77 tertiary hospitals in China. *PLoS One* **9**: e103507

PLoS One

Association between BMI and mortality in older people

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 The "obesity paradox", in which overweight or obese individuals appear to have a lower risk of death than those with a healthy or low weight, is well documented; however, there is debate as to whether these findings can be applied to older people.

2 These authors evaluated the association of BMI with mortality in a large cohort of 77 541 people from Taiwan aged ≥65 years (mean, 73.1 years) over a 5-year follow-up.

3 There were 3842 deaths (5% of the cohort); of these, 877 (22.8%) were due to cardiovascular disease (CVD) and 1116 (29.0%) were due to "expanded CVD" (defined as CVD, diabetes or kidney disease).

4 The relationship between BMI and all-cause, CVD and expanded CVD mortality appeared to have a U-shaped curve, with underweight (hazard ratios [HRs], 1.92, 1.74 and 1.77, respectively) and grade 2–3 obese people (HRs, 1.59, 2.36 and 2.22) having an increased risk of death compared with people of normal weight.

5 Conversely, overweight and grade 1 obese people had reduced mortality risk (HRs, 0.75–0.90 across the difference causes of death).

6 When all three categories of obesity were combined into a single group, a reduced mortality risk was observed, presumably because mildly obese people outnumbered severely obese people.

7 Given this U-shaped association, unilateral promotion of weight loss in older people may be inappropriate, and grade 1 obesity confers a different mortality risk than more severe grades.

Wu CY, Chou YC, Huang N et al (2014) Association of body mass index with all-cause and cardiovascular disease mortality in the elderly. *PLoS One* **9**: e102589

PLoS One

Adiposity indices other than BMI

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 The accuracy of BMI in predicting cardiovascular disease, diabetes or mortality is questionable compared with other measures of adiposity.

2 In this study, the association between various anthropometric indices (BMI, waist circumference, waist-to-height ratio [WHtR] and height) and all-cause mortality was assessed in a cohort of older patients at high cardiovascular risk.

3 A total of 7447 participants (age, 55–80 years; 43% men) taking part in a study to assess the effects of a Mediterranean diet were evaluated over a median follow-up of 4.8 years.

4 In the multivariate analysis, WHtR and waist circumference were directly associated with mortality; however, the association between BMI and mortality was not significant.

5 In general, when participants were stratified according to gender, the associations between anthropometrics and mortality were only significant for women; however, no significant interaction with gender was found.

6 When using *a priori* cut-off points for WHtR of 0.60, 0.65 and 0.70, the hazard ratios (HRs) for death were 1.02, 1.30 and 1.55, respectively, compared with a WHtR of <0.60. With cut-offs for waist circumference of 100, 105 and 110 cm, the HRs were 1.18, 1.02 and 1.57, respectively, compared with a waist circumference of <100 cm.

7 Given that there was also a relationship between height and mortality, the authors suggest that WHtR is the best predictor of mortality in elderly people at high cardiovascular risk. The association between WHtR and death was stronger in people with diabetes.

Martínez-González MA, García-Arellano A, Toledo E et al (2014) Obesity indexes and total mortality among elderly subjects at high cardiovascular risk: the PREDIMED study. *PLoS One* **9**: e103246

"The results confirm that suboptimal glycaemic control, even when achieving an HbA_{1c} of <7%, affects the likelihood of achieving American Diabetes Association targets for blood pressure."