Cardiovascular and major journals

Good glycaemic control does improve major CV outcomes: It's time to pursue national diabetes care targets with vigour

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The ACCORD (Action to Control Cardiovascular Risk in Diabetes) and VADT (Veterans Affairs Diabetes Trial) studies sowed seeds of doubt in the minds of many clinicians in diabetes care by appearing to show that intensive glycaemic control caused deaths in people with type 2 diabetes (ACCORD Study Group, 2008; Duckworth et al, 2009). Caution was exercised when dealing with poor glycaemic control and clinical inertia was evident, irrespective of whether this association was causal or not.

Fang and colleagues have shed more light on this matter, performing a meta-analysis with rigorous methodology on 13 studies of intensive glycaemic control versus conventional treatment (summarised alongside). They conclude that intensive glycaemic control is safe, with a mixed bag of distinct clinical benefits. There was actually no improvement in mortality rates; the relative risk with intensive treatment was a non-significant 0.98. Similarly, cardiac deaths, congestive heart failure and stroke were not improved – but, more importantly, not worsened – by intensive glycaemic control. However, the overall conclusion from the 58 160 people studied was that the rate of major adverse cardiac events (MACE) and myocardial infarction were significantly reduced by 8% and 10%, respectively.

There was always a debate whether the rapid improvement in glycaemic control in people with a long duration of diabetes, using multiple agents, was the actual cause of the problem in ACCORD and VADT. The average duration of diabetes in ACCORD was 10 years. In contrast to these trials, better clinical accounts of intensive or improved glycaemic control emerged in trials that enrolled people at the onset of their diabetes, such as the UKPDS (UK Prospective Diabetes Study Group, 1998). It was also clear from the meta-analysis that studies involving multifactorial interventions, such as Steno-2 (Gaede et al, 2008) and UKPDS (which had blood pressure [BP] and glycaemic control arms), had the best outcomes in terms of reducing all diabetes complications, including MACE.

Previous research from the Clinical Practice Research Datalink concluded that all-cause mortality, stroke mortality and coronary mortality were lowest in people who were in the "good control" range for all three major CVD risk factors (Kontopantelis et al, 2015). These were found to be an HbA_{1c} of 56–61 mmol/mol (7.25–7.75%), a total cholesterol of 3.5–4.5 mmol/L, a systolic BP of 135–145 mmHg and a diastolic BP of 82.5–87.5 mmHg. The latest National Diabetes Audit shows that only 18.1% of people with type 1 and 40.2% of those with type 2 diabetes reach these targets in clinical practice in the UK (NHS Digital, 2017). We would serve our patients better by ensuring that the vast majority attain these targets to reduce the risk of all complications of diabetes. It is time to accept this diktat and pursue national diabetes care targets with renewed enthusiasm. ■

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

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

Gaede P, Lund-Andersen H, Parving HH, Pedersen O (2008) Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* **358**: 580–91

Kontopantelis E, Springate DA, Reeves D et al (2015) Glucose, blood pressure and cholesterol levels and their relationships to clinical outcomes in type 2 diabetes: a retrospective cohort study. *Diabetologia* **58**: 505–18

NHS Digital (2017) *National Diabetes Audit – 2015–2016: Report 1. Care processes and treatment targets.* NHS Digital, Leeds. Available at: http://bit.ly/2kZOW7T (accessed 17.02.17)

UK Prospective Diabetes Study Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **352**: 837–53

Int J Cardiol

Effects of intensive glucose lowering on CV outcomes in T2D: Meta-analysis

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

1 These authors conducted a meta-analysis of available randomised controlled trials (RCTs) to evaluate the effect of intensive glucose-lowering therapy on cardiovascular (CV) risk in people with T2D, and to compare outcomes in different subpopulations.

2 In total, 13 RCTs with 58 160 participants were evaluated. In the pooled analysis, intensive therapy had no significant effect on total or CV mortality, stroke or congestive heart failure.

3 However, intensive treatment did have a beneficial effect on the risk of myocardial infarction (MI; relative risk [RR], 0.90; 95% confidence interval [CI], 0.82–0.98) and a composite of major adverse cardiac events (MACE; RR, 0.92; 95% CI, 0.85–1.00).

4 Subanalysis revealed that intensive treatment had an effect on MACE in trials with <70% male participants (RR, 0.93), a median diabetes duration of ≥10 years (RR, 0.90) and a median systolic blood pressure (BP) of ≥140 mmHg (RR, 0.82).

5 Intensive treatment was associated with reduced overall and CV mortality rates in people with a diastolic BP ≥80 mmHg and those with an LDL-cholesterol level ≥3 mmol/L.

6 These important baseline characteristics that may modify the effects of intensive treatment should be verified in future large-scale RCTs.

7 In conclusion, intensive therapy improves the risk of MACE and MI, without increasing mortality, in T2D.

Fang HJ, Zhou YH, Tian YJ et al (2016) Effects of intensive glucose lowering in treatment of type 2 diabetes mellitus on cardiovascular outcomes: a meta-analysis of data from 58,160 patients in 13 randomized controlled trials. *Int J Cardiol* **218**: 50–8

Int J Cardiol

RAS blockers reduce dementia risk in people with T2D and hypertension

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

1 Some antihypertensive drugs have been reported to help prevent dementia. Given the known links between hypertension, T2D and dementia risk, these authors conducted a large, population-based cohort study to assess the effects of renin–angiotensin system (RAS) blockers on dementia risk in people with T2D and hypertension.

2 The Taiwan National Health Insurance Research Database was used to identify all people aged ≥50 years, with a new T2D diagnosis between January 2000 and December 2011, and with a history of hypertension before their T2D diagnosis.

3 In total, 2377 people receiving angiotensin-converting enzyme inhibitors (ACEIs) and 1780 receiving angiotensin receptor blockers (ARBs) were compared with the same number of propensity-score-matched people not receiving ACEIs and ARBs, respectively.

4 Over the 12-year follow-up, the cumulative incidence of all-cause dementia was significantly lower in both ACEI recipients (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.56–0.96) and ARB recipients (HR, 0.60; 95% CI, 0.37–0.97).

5 The effects were mostly driven by reductions in vascular dementia, while Alzheimer's disease risk was not significantly affected.

6 Cumulative dosage was inversely associated with dementia risk.

7 ARBs appeared to be superior to ACEIs in preventing dementia.

Kuan YC, Huang KW, Yen DJ et al (2016) Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers reduced dementia risk in patients with diabetes mellitus and hypertension. *Int J Cardiol* **220**: 462–6

Cardiovasc Diabetol

Moderate-intensity statins for primary CVD prevention in people with T2D and nephropathy

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

1 These authors evaluated the use of statins in a cohort of people with T2D complicated by nephropathy, to determine their efficacy in primary prevention of cardiovascular disease (CVD) in this high-risk population.

2 In an observational, prospective study, 564 people with T2D and free of CVD at study initiation were followed up for 8 years. Of these, 169 were treated with statins and 395 were not.

3 Notably, none of the participants received high-intensity statins, suggesting that clinicians were treating to target rather than according to American Diabetes Association guidelines.

4 Total major adverse cardiac event (MACE) rates were 2.37 and 2.15 per 100 person-years in statin recipients and non-recipients, respectively.

5 Kaplan–Meier survival curves showed a non-significant difference in the incidence of total MACE in the two groups (P=0.758).

6 No significant differences in other CVD risk factors (BMI, HbA_{1c}, blood pressure, triglycerides or kidney function) were observed at the 8-year follow-up.

7 The authors conclude that moderate-intensity statins are ineffective for primary CVD prevention in people with T2D and nephropathy. They add that multifactorial intervention is required to reduce the residual risk.

Sasso FC, Lascar N, Ascione A et al (2016) Moderate-intensity statin therapy seems ineffective in primary cardiovascular prevention in patients with type 2 diabetes complicated by nephropathy. A multicenter prospective 8 years follow up study. *Cardiovasc Diabetol* **15**: 147

Int J Cardiol

High- versus moderate-intensity statins in people with ACS and T2D

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

1 This randomised controlled trial was performed to compare high- and moderate-intensity statin treatment in people with acute coronary syndrome (ACS) and T2D.

2 In total, people with ACS and T2D who underwent primary or early percutaneous coronary intervention (PCI), and who had not received long-term statins before PCI, were randomised to receive atorvastatin 40 mg/day (n=297) or 20 mg/day (n=294) following the procedure.

3 In the first 30 days following PCI, there was a non-significant trend towards a lower rate of major adverse cardiac events (MACE) in the 40 mg group.

4 After 1 year, MACE risk was significantly lower in the 40 mg group (8.4% vs 14.6%; hazard ratio, 0.61; 95% confidence interval, 0.36–0.91).

5 Regarding individual MACE outcomes, spontaneous myocardial infarction (2.7% vs 6.1%; P=0.04) and stroke (3.4% vs 6.8%; P=0.05) had the greatest reductions; however, the rates of death and revascularisation also trended towards lower rates.

6 The authors note that this was a single-centre study with a modest sample size, and that concordance with medications other than atorvastatin was not assessed.

7 Despite these limitations, they conclude that high-intensity statins are superior in improving the long-term prognosis of people with ACS and T2D.

Liu Z, Xu Y, Hao H et al (2016) Efficacy of high intensity atorvastatin versus moderate intensity atorvastatin for acute coronary syndrome patients with diabetes mellitus. *Int J Cardiol* **222**: 22–6

"Intensive therapy improves the risk of major adverse cardiac events and myocardial infarction, without increasing mortality, in T2D."