Cardiovascular and major journals

The effect of glucose-lowering therapies on cardiovascular health

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The main cause of death in T2D remains cardiovascular disease (CVD), and hyperglycemia is associated with increased CV risk. However, the benefits of intensive blood glucose reduction with respect to cardiovascular (CV) outcomes have been disappointing, with such benefits being potentially confounded by weight gain and hypoglycaemia. There are multiple novel blood glucose-lowering therapies, targeting multiple pathophysiological components of T2D, which are associated with varying degrees of hypoglycaemia and weight gain. It is, however, unknown whether a specific glucose-lowering therapy is superior to other drugs in reducing cardiovascular outcomes in T2D.

This study by Geji et al (summarised alongside) used a nested case–control methodology to evaluate this question, with a specific focus on glucagon-like peptide (GLP)-1 analogues and biguanides as these agents have been reported to exert multiple physiological effects, which may beneficially influence the natural history of CVD in T2D. Cases were people with T2D who experienced CV events (defined as a composite of ischaemic heart disease, heart failure or stroke) and controls were people who had no history of CVD after T2D diagnosis. Over 10 000 people with T2D were included in the study, and nearly 2000 experienced a subsequent CV event. Experiencing one of the composite endpoints prior to diabetes diagnosis increased the risk of further CV events (odds ratio, 20.18 [95% confidence interval, 16.88–24.12]). Neuropathy and peripheral artery disease also increased this risk. Taking biguanides and liraglutide significantly decreased the risk of CV events, as did statin treatment. Dipeptidyl peptidase-4 inhibitors, insulin and beta-cell-stimulating agents, which were also investigated, exhibited a neutral effect on CV risk.

Even after adjustment for biochemical risk markers, biguanides and liraglutide treatment continued to exert a significant risk reduction on the composite endpoint, suggesting pleiotropic, beneficial effects on the risk of developing ischaemic heart disease, stroke or heart failure, in addition to the effect on glucose control and cholesterol, for example.

Exenatide (another GLP-1 analogue) was shown to not reduce the risk of composite endpoint in the study, which is surprising as a previous study had revealed no difference in CVD risk between the exenatide and liraglutide treatments (Monami et al, 2011). In addition, it has been reported that exenatide treatment had a lower risk of CVD events compared with other glucose-lowering therapies (Best et al, 2011). The difference observed in the study by Geji et al may be explained by inherent differences in the pharmacological effects of exanatide and liraglutide as they differ in molecular structure and pharmacokinetic and pharmacodynamic profiles. It could also be due to the power of the study, as fewer people were treated with exenatide than liraglutide.

Limitations of the study noted by the authors include its retrospective design, which means causality cannot be evaluated, and important information on modifiable CV risk factors (e.g. smoking, physical activity, diet and weight) were not available, which may exert an effect. The method of control selection, inclusion of prevalent users, and channelling of sicker individuals into the reference group for liraglutide users could also potentially bias the results.

Nevertheless, these results provide an important insight into the possible CV effects of blood glucose-lowering therapies while the results of long-term studies specifically directed at assessing CV safety in relation to different blood glucose-lowering therapies are awaited. ■

Best JH, Hoogwerf BJ, Herman WH et al (2011) Risk of cardiovascular disease events in patients with type 2 diabetes prescribed the glucagon-like peptide 1 (GLP-1) receptor agonist exenatide twice daily or other glucose-lowering therapies: a retrospective analysis of the LifeLink database. *Diabetes Care* **34**: 90–5

Monami M, Cremasco F, Lamanna C et al (2011) Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. *Exp Diabetes Res* **2011**: 215764

Int J Cardiol

Diabetes treatments: Their effect on reducing cardiovascular risk

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

1 The effects of diabetes treatments on the composite endpoint (CE) of ischaemic heart disease, heart failure or stroke in people with T2D were investigated in a large nested case–control study in Denmark. In total, 10 073 people were included (65 550 person-years) and data on medication use and biochemical parameters were collected.

2 Cases were people with T2D who went on to experience CE, and the controls were people with no history of CE after the T2D diagnosis.

3 In total, 1947 cases experienced a subsequent CE. CE before diagnosis (odds ratio [OR], 20.18 [95% confidence interval (CI), 16.88–24.12]), nephropathy and peripheral artery disease increased the risk of CE.

4 Biguanides (OR, 0.62 [95% CI, 0.54–0.71]) and liragutide (OR, 0.48 [95% CI, 0.38–0.62]) both significantly decreased the risk of CE, and continued to exert a significant reduction in risk after adjustments for biochemical markers. The effect of liraglutide was dose and duration dependent ($P<0.05$). Dipeptidyl peptidase-4 inhibitors, insulin and beta-cell-stimulating agents had a neutral effect on CV risk. Statin treatment, which lowers cholesterol, also reduced the risk of CE.

5 The authors showed that biguanides and liraglutide reduce the risk of CE in people with T2D.

Gejl M, Starup-Linde J, Scheel-Thomsen J et al (2015) Risk of cardiovascular disease: the effects of diabetes and anti-diabetic drugs – a nested case-control study. *Int J Cardiol* **178**: 292–6

Am J Hypertens

Three interventions on systolic blood pressure

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

1 In an across-study analysis, the relative effectiveness of three approaches to systolic blood pressure (SBP) control were investigated among overweight and obese adults with T2D.

2 The three approaches were intensive lifestyle intervention (ILI) focused on weight gain; frequent goal-based monitoring of blood pressure with pharmacological management; and, education and support.

3 In total, 480 people from the Action for Health in Diabetes (Look AHEAD) study and 1129 people from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study were included. These individuals met the clinical criteria of both clinical trials and had baseline SBP between 130 and 159 mmHg.

4 The proportion of individuals with SBP <140 mmHg from annual standardised assessments over time were compared with generalised estimating equations.

5 Across 4 years, ILI (odds ratio [OR], 1.46 [95% confidence interval (CI), 1.18–1.81]) and frequent goal-based monitoring with pharmacotherapy (OR, 1.51 [95% CI, 1.16–1.97]) yielded higher rates of SBP control compared to education and support.

6 The authors also suggested that intensive behavioural-based intervention may have been more effective among those with a BMI >30 kg/m^2, while frequent goal-based monitoring with medication management may be more effective for individuals with a lower BMI.

Espeland MA, Probstfield J, Hire D et al (2015) Systolic blood pressure control among individuals with type 2 diabetes: a comparative effectiveness analysis of three interventions. *Am J Hypertens* 9 Feb [Epub ahead of print]

JAMA

What role does glycaemic index play on CV and T2D?

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

1 The authors aimed to determine the effect of glycaemic index (GI) of different diets on risk factors for cardiovascular (CV) disease and T2D.

2 A randomised crossover-controlled feeding trial across multiple medical centres involved 163 overweight adults eating at least two complete diets each for 5 weeks.

3 The four possible diets included all meals, snacks and calorie-containing beverages: (1) A high GI (65% on the glucose scale), high-carbohydrate diet (58% energy); (2) a low-GI (40%), high-carbohydrate diet; (3) a high-GI, low-carbohydrate diet (40% energy); and (4) a low-GI, low-carbohydrate diet.

4 The investigated outcomes included insulin sensitivity, insulin levels during an oral glucose tolerance test, systolic blood pressure and cholesterol and triglyceride levels.

5 At high dietary carbohydrate content, the low-GI diet compared with high-GI diet decreased insulin sensitivity from 8.9 to 7.1 units (P=0.002), increased LDL-cholesterol from 139 to 147 mg/dL (3.6 to 3.8 mmol/L; $P\leq$0.001); and did not affect HDL-cholesterol, triglycerides or blood pressure.

6 At low-carbohydrate content, the low-GI diet compared with high-GI diet only decreased triglycerides from 91 to 86 mg/dL (2.4 to 2.2 mmol/L; P=0.02).

7 Low-GI diets compared to high-GI diets did not result in improvements in the investigated measures. Using the GI to select foods may not improve CV risk factors or insulin resistance.

Sacks FM, Carey VJ, Anderson CA et al (2014) Effects of high vs low glycemic index of dietary carbohydrate on cardiovascular disease risk factors and insulin sensitivity: the OmniCarb randomized clinical trial. *JAMA* **17**: 2531–41

Am J Cardiol

Statin therapy on incident T2D among those who have high or low risk of T2D

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

1 There have been reports of increased incidence of T2D in people using statins, although it is unclear whether this only applies to those already at high risk for developing T2D, or whether this can apply to anyone.

2 In this prospective cohort study, 4645 people with established vascular disease without T2D were included. In total, 3057 people used statins at baseline, and 1608 used intensive statins therapy.

3 Statin therapy was associated with an increased risk of incident T2D among people with clinically manifest vascular disease when adjusted for age, gender, BMI, and plasma HDL-cholesterol and triglyceride levels (hazard ratio [HR], 1.63 [95% confidence interval (CI), 1.15–2.32]).

4 Intensive statin therapy tended to be related to a higher T2D risk compared to moderate statin therapy (adjusted HR, 1.22 [95% CI, 0.92–1.61]).

5 The observed increase in T2D risk was independent of the number of metabolic syndrome characteristics the participants had. This suggests that statin use can cause incident T2D in people who do not have a high risk of T2D.

6 In fact, the increased risk of T2D was particularly apparent in people with low baseline glucose (<5.6 mmol/L).

van de Woestijne AP, van der Graaf Y, Westerink J et al (2015) Effect of statin therapy on incident type 2 diabetes mellitus in patients with clinically manifest vascular disease. *Am J Cardiol* **15**: 441–6

"The nested case–control study demonstrated a reduced risk of a composite of ischemic heart disease, heart failure and stroke with the use of biguanides or liraglutide in people with T2D."