Diabetes journals

Reassuring data on safety of exenatide in reducing the incidence of CVD events

Marc Evans, Consultant Physician, Llandough Hospital, Cardiff

In this retrospective database analysis, Best et al (2010; summarised alongside) sought to test the hypothesis that treatment with exenatide reduces the relative incidence of cardiovascular disease (CVD) events among people with type 2 diabetes compared with other blood glucose-lowering agents. People with no history in the preceding 9 months of CVD events were assigned to the exenatide-initiated or non-exenatide-initiated cohorts, and reassigned if exenatide was prescribed or discontinued. Myocardial infarction, ischaemic stroke or coronary revascularisation procedure were identified, and participants' outcomes adjusted for differences in clinical and demographic characteristics and compared.

People receiving exenatide were 19% less likely to have a CVD event than people treated with other blood glucose-lowering agents; people in the exenatide group were also less likely to experience CVD-related and all-cause hospitalisation. The results support the CVD safety of twice-daily exenatide for people with type 2 diabetes.

When evaluating the results there are a variety of issues that need to be considered. In particular, the absence of randomisation, which can result in different demographic profiles arising between groups and hence introduce so-called "allocation bias" into the results. In this study, lipid levels, blood pressure, obesity and evidence of prior CVD were higher in people initially treated with exenatide than in those initially treated with other agents. Also, use of lipid-lowering agents, angiotensin-converting enzyme inhibitors, general antihypertensive agents and multiple antidiabetes therapies were higher in people receiving exenatide. This could introduce a variable that is difficult to control for, namely that physicians might be using newer agents such as exenatide in people with more "severe" type 2 diabetes and managing them more intensively. Another factor to consider is the impact of incomplete data capture (e.g. smoking, alcohol consumption). These represent major limitations when evaluating these data.

Nevertheless, this analysis provides reassuring CVD safety data for exenatide, including a greater reduction of hyperglycaemia with less hypoglycaemia and/or improvement in CVD risk factors. However, a randomised, controlled, clinical trial of the cardiovascular outcomes associated with long-term use of exenatide is needed to demonstrate whether treatment with this agent reduces CVD risk.

DIABETOLOGIA

Metformin linked to lower mortality risk in heart failure

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

1 To determine the safety of metformin treatment in people with T2D and heart failure (HF), 10 920 people with T2D who were hospitalised for first-time HF and treated with metformin, sulphonylureas and/or insulin were followed-up for a median of 844 days.

2 In total, 6187 people died during the follow-up.

3 Compared with a sulphonylurea monotherapy, an improved outcome was observed with metformin monotherapy (hazard ratio [HR], 0.85; 95% confidence interval (CI), 0.75–0.98; P=0.02) and with metformin in combination with a suphonylurea (HR, 0.89; 95% CI, 0.82–0.96; P=0.003).

4 People with HF and T2D treated with metformin had a lower mortality risk than those treated with a suphonylurea or insulin alone in this cohort.

Andersson C, Olesen JB, Hansen PR et al (2010) Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. *Diabetologia* **53**: 2546–53

DIABETES CARE

Exenatide reduces risk of CVD events in people with T2D

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

1 The risk of cardiovascular disease (CVD) is increased up to five-fold in people with T2D compared with those without T2D; studies report that hyperglycaemia is associated with an increased risk of CVD.

2 Few data exist on the effects of antidiabetes agents on CVD events; additionally, newer treatments, such as exenatide, have no data on their effects on CVD outcomes.

3 The authors retrospectively analysed the risk of a first CVD event among people with T2D treated with twice-daily exenatide (n=39 275) or other blood glucose-lowering therapies (n=381 218) from the LifeLink database (June 2005–March 2009).

4 People in the exenatide-treated group were more likely to have a history of ischaemic heart disease, obesity, hyperlipidaemia, hypertension or other comorbidities at baseline.

5 Results showed that people treated with exenatide were significantly less likely to have a CVD event than those treated with other blood glucose-lowering therapies (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.68–0.95; P=0.01), and people treated with exenatide had lower rates of CVD-related hospitalisation (HR, 0.88; 95% CI, 0.79–0.98; P=0.02) and all-cause hospitalisation (HR, 0.94; 95% CI, 0.91–0.97; P<0.001).

6 The authors found that these results supported the hypothesis that exenatide reduces the risk for CVD events, and CVD-related hospitalisation, in people with T2D.

Best JH, Hoogwerf BJ, Herman WH et al (2011) Risk of cardiovascular disease events in patients with T2D prescribed the GLP-1 receptor-agonist exenatide twice-daily or other glucose-lowering therapies. *Diabetes Care* **34**: 90–5

DIABETES CARE

Intensive glycaemic control may not be suitable for those with T2D and CVD

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

1 Although it is known that tighter glycaemic control and lower HbA_{1c} levels decrease the risk of microvascular complications, it is unclear what the ideal HbA_{1c} target is for minimising cardiovascular disease (CVD) events in people with T2D.

2 A nested case-control design was used to determine the relationship between glycaemic control and CVD events in 11 157 people with T2D matched to 44 628 controls over 3 years.

3 People with T2D with an average HbA_{1c} level ≤6% (≤42 mmol/mol) were 20% more likely to experience a CVD event than those with an HbA_{1c} >6–8% (>42–64 mmol/mol), while those with an average HbA_{1c} level >8% (>64 mmol/mol) were 16% more likely to experience a CVD event than those with an HbA_{1c} level >6–8% (>42–64 mmol/mol; both $P<0.0001$).

4 Compared with the control group, people treated with insulin were at a 2.5-fold increased risk of a CVD event and people treated with sulphonylurea monotherapy or other combinations of oral therapy were at a 55% increased risk of a CVD event; metformin monotherapy was not associated with an excess CVD risk.

5 Antipsychotic agents, erythropoiesis-stimulating agents and tricyclic antidepressants were linked with an increased CVD risk.

6 The authors concluded that intensive HbA_{1c} lowering may not be appropriate for all people with T2D and that individual CVD risk profiles should be considered when developing a treatment regimen.

Colayco DC, Niu F, McCombs JS, Cheetham TC (2011) Glycosylated haemoglobin and cardiovascular outcomes in type 2 diabetes. *Diabetes Care* **34**: 77–83

DIABETOLOGIA

Screening for T2D reduces mortality

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

1 The authors assessed the effect of population screening for T2D on mortality, with long-term follow-up of 4936 people (aged 40–65 years).

2 People were randomly divided into three groups: one-third were invited to T2D screening in 1990–92; one-third were invited to T2D screening in 2000–03; and one-third were not invited to screening at any time.

3 Compared with those who were not invited to screening, invitation to T2D screening in 1990–92 was associated with a 21% reduction in all-cause mortality; however, there was no significant difference in mortality between the non-invited group and the group invited to T2D screening in 2000–03.

4 Overall, compared with the non-invited group, people who were screened for T2D at any time had a significantly lower mortality.

Simmons RK, Rahman M, Jakes RW et al (2010) Effect of population screening for type 2 diabetes on mortality: long-term follow-up of the Ely cohort. *Diabetologia* [Epub ahead of print]

DIABETOLOGIA

Postprandial TG associated with increased risk of CVD

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

1 The study aim was to determine the effect of postprandial time on the associations between lipid concentrations and cardiovascular disease (CVD) in 1337 people with diabetes.

2 Baseline measures included total, LDL- and HDL-cholesterol and triacylglycerol (TG) concentrations; participants were followed-up for incidence of CVD for a mean of 8 years.

3 Correlations between postprandial time and lipid concentrations were only significant for TG, which declined from a mean 1.86 mmol/L at 0.1 hour to 1.33 mmol/L at >6 hours ($P<0.001$).

4 Increased TG concentrations were found to be associated with increased risk of CVD, independent of postprandial time; however, postprandial time did not influence the association of lipid concentrations with CVD in people with diabetes.

van Dieren S, Nöthlings U, van der Schouw YT et al (2011) Non-fasting lipids and risk of cardiovascular disease in patients with diabetes mellitus. *Diabetologia* **54**: 73–7

DIABETES CARE

Metformin reduces cancer risk in T2D

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

1 The authors of this study sought to determine the effect of metformin on cancer incidence in a cohort of 1340 people with T2D and no history of malignancies who had commenced insulin therapy.

2 During a median follow-up of 75.9 months there were 112 cases of incident cancer; 370 controls were matched for age, sex and BMI from the same cohort.

3 There were significantly fewer people on metformin or sulphonylureas among the cases during follow-up; after adjustments, people treated with meformin, but not sulphonylureas, had a reduced incidence of cancer.

4 The authors concluded that this reduction in cancer risk supports maintaining metformin in people with T2D treated with insulin, in addition to the beneficial effects of metformin on insulin sensitivity, insulin dose and glucose control.

Monami M, Colombi C, Balzi D et al (2011) Metformin and cancer occurrence in insulin-treated type 2 diabetic patients. *Diabetes Care* **34**: 129–31

> ***"Results showed that intensive HbA_{1c} lowering may not be appropriate for all people with T2D as individual cardiovascular risk profiles should be considered."***