Major and cardiovascular journals

Cardiovascular safety data published: This time, sitagliptin

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Good glycaemic control is an important factor with respect to the long-term risk of both micro- and macrovascular complications in people with type 2 diabetes (Holman et al, 2008). There is a large array of glucose-lowering therapies, with a rapid proliferation of novel agents. Following the experiences with rosiglitazone some 10 years ago (Nissen and Wolski, 2007), international regulatory agencies have focused on the long-term cardiovascular safety of glucose-lowering therapies in T2D. Sitagliptin, an orally administered dipeptidyl peptidase-4 (DPP-4) inhibitor, exerts its glucose-lowering effects through prolonging the bioavailability of the incretin hormone glucagon-like peptide-1. The cardiovascular outcome and safety trial of sitagliptin is summarised alongside.

As part of TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) over 14 000 participants were assigned placebo or sitagliptin added to usual care, and the primary outcome under observation was a composite of major cardiovascular events. With the aim for individually appropriate glycaemic targets to be reached, open-label use of glucose-lowering therapy was encouraged as required.

During a median follow-up of 3 years, there was little difference in HbA_{1c}, rates of hospitalisation for heart failure, or acute pancreatitis or pancreatic cancer between the sitagliptin and placebo arms of the study. There was also little difference in the frequency of the primary outcome occurring between the two study groups, and, as such, sitagliptin was shown to be non-inferior to placebo for the primary composite cardiovascular outcome. The data from this study thus suggest that sitagliptin does not affect the cardiovascular risk of users when added to usual care.

Two previous cardiovascular outcome trials of other DPP-4 inhibitors did not show an increase or decrease in the number of major adverse cardiovascular events, but they did raise safety concerns regarding a possible elevated risk of hospitalisation for heart failure (Scirica et al, 2013; White et al, 2013). Meta-analyses of randomised, controlled trials since have suggested an increase of 24–25% in such a risk associated with these agents (Clifton, 2014; Udell et al, 2015). This was not observed in the case of sitagliptin, and the authors concluded this could be down to differences in participant characteristics, in care prior to the study, in the recording and definition of heart failure events, in the pharmacological differences between the DPP-4 inhibitors or it may represent the role of chance in previous findings. Of note, the patient population in TECOS tended to have a shorter duration of diabetes and lower baseline HbA_{1c} levels than previous DPP-4 inhibitor cardiovascular safety trials.

Other important considerations when assessing the implications of the TECOS were highlighted by the authors. Firstly, there was an opportunistic approach to data collection of measures other than HbA_{1c}; therefore, the study can not provide any definitive information on the effects of sitagliptin on factors such as urinary albumin excretion. Secondly, there may be potential confounding effects on cardiovascular outcomes by the small residual between-group difference in HbA_{1c}. Thirdly, there was a greater use of glucose-lowering agents in the placebo group.

Despite the limitations, the results of this study would appear to have wide-ranging generalisability, given that it was carried out in a usual-care setting and included people with a global distribution. In essence, this study shows that sitagliptin may be used in a diverse group of people with type 2 diabetes who are at high cardiovascular risk without increasing rates of cardiovascular complications. However, these results cannot say what will happen with a longer duration of therapy or what the efficacy will be in people with more complicated co-existing illnesses. ■

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N Engl J Med

Sitagliptin: Cardiovascular safety trial

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

1 The long-term cardiovascular (CV) safety of glucose-lowering, T2D medication is an ongoing area of research. In this study, the CV safety of sitagliptin, a dipeptidyl peptidase-4 inhibitor, was under investigation.

2 In a randomised, double-blind study, 14 671 people were assigned to either sitagliptin or placebo to usual care.

3 The primary CV outcome was a composite of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for unstable angina.

4 Over a median follow-up of 3.0 years, there was a small difference in HbA_{1c} between the sitagliptin and placebo group, and a similar number of people in the sitagliptin and placebo groups (839 [11.4%] and 851 [11.6%] respectively) experienced the primary CV outcome. Sitagliptin was shown to be non-inferior to placebo for the primary composite outcome (hazard ratio, 0.98; 95% confidence interval, 0.88–1.09; $P<0.001$ [a relative risk of 1.3 was the marginal upper boundary]).

5 Rates of hospitalisation for heart failure did not differ between the two groups ($P=0.98$), and neither did the rates of acute pancreatitis ($P=0.07$) nor pancreatic cancer ($P=0.32$).

6 Adding sitagliptin to the therapy regimen did not appear to increase the risk of major CV events, hospitalisation for heart failure or other CV events of individuals with T2D when added to usual care.

Green JB, Bethel MA, Armstrong PW et al (2015) Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* **373**: 232–42

N Engl J Med

Follow-up CV and mortality data from VADT

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

1 The VADT (Veterans Affairs Diabetes Trials) showed that intensive glucose lowering did not improve the risk of major cardiovascular (CV) events compared to standard care in nearly 1800 military veterans. The research group followed the participants for a median of 3 years and now present long-term follow-up data.

2 The authors had complete and follow-up data for 92.4% of the participants, which was collected by annual surveys and chart reviews.

3 The primary outcome under investigation was time to first major CV event and the secondary end-points were CV mortality and all-cause mortality.

4 By 3 years after the VADT ended, the difference in HbA_{1c} between the intensive- and standard-care group had diminished to 0.2–0.3%. During the trial, it had been 16.4 mmol/mol (1.5%) lower in the intensive-therapy group than the standard-therapy group.

5 Across the total median follow-up of 9.8 years, the intensive-therapy group had a significantly lower risk of the primary outcome of major CV events than the standard-therapy group, but there was no difference or reduction in CV or all-cause mortality between the two study groups.

6 Although no improvement was seen to overall survival in the intensive-therapy arm, participants in this group had 8.6 fewer major CV events per 1000 person-years than those assigned to standard therapy.

Hayward RA, Reaven PD, Wiitala WL et al (2015) Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* **372**: 2197–206

Eur Heart J

Comparative drug data for heart failure hospitalisation

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

1 In this retrospective study, the risk of hospitalisation due to heart failure (HF) in respect to glucose-lowering medication was investigated to ascertain if there were differences among drug classes.

2 In total, 32 Health Services of 16 Italian regions were included, which comprised a total population of 18 million individuals.

3 The end-point under investigation was hospitalisation for HF (HHF) occurring after the first 6 months of treatment and up to 4 years later.

4 Over 127 000 unmatched people with T2D were included: 14.3% were on dipeptidyl dipeptidase-4 (DPP-4) inhibitor, 72.5% on sulphonylurea (SU) and 13.2% on thiazolidinediones (TZD) alone; 70.7% were on metformin as combination therapy.

5 The baseline characteristics for the treatment groups were significantly different. In particular, previous cardiovascular events occurred significantly more often in the DPP-4 inhibitor group compared to both the SU and TZD groups.

6 During an average follow-up of 2.6 years, DPP-4 inhibitor use was associated with a reduced risk of HHF compared with SUs (hazard ratio, 0.78; 95% confidence interval, 0.62–0.97; $P=0.026$). The association was still observed after propensity matching of 39 465 individuals.

7 Compared to SU use, the use of DPP-4 inhibitors was associated with a reduced risk of HHF.

Fadini GP, Avogaro A, Degli Esposti L et al (2015) Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications. *Eur Heart J* **36**: 2454–62

BMJ

T2D prediction: Birth weight and later lifestyle adherence

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

1 The authors aimed to prospectively assess the joint association of birth weight and established lifestyle risk factors with incident T2D. They investigated their separate effects and also their interaction.

2 In total, 149 794 men and women without diabetes, cardiovascular disease or cancer at baseline were selected from cohorts of established studies: the Health Professionals Follow-up Study, Nurses' Health Study and Nurses' Health Study II.

3 To measure the incidence of T2D, self-reported questionnaires were used and unhealthy lifestyle factors were measured by consulting BMI, physical activity levels, alcohol consumption and smoking, and the alternate healthy eating index.

4 Over a long follow-up period of 20–30 years, 11 709 new cases of T2D were documented. Following multivariate analysis, the relative risk of T2D was 1.45 (95% confidence interval [CI], 1.32–1.59) per kg lower birth weight, and 2.10 (95% CI, 1.71–2.58) per unhealthy lifestyle factor.

5 The combination of per kg lower birth weight and per unhealthy lifestyle factor had a relative risk of T2D of 2.86 (95% CI, 2.26–3.63). This was more than the addition of the risks associated with each individual factor, which suggests the strength of the additive interaction of low birth weight and unhealthy life factors.

6 This study highlights the importance of a healthy lifestyle and the impact of prenatal factors on later life outcomes.

Li Y, Ley SH, Tobias DK et al (2015) Birth weight and later life adherence to unhealthy lifestyles in predicting type 2 diabetes: prospective cohort study. *BMJ* **351**: h3672

"The study highlights the importance of a healthy adult lifestyle and the impact of prenatal factors on outcomes in later life."

References from commentary

Clifton P (2014) Do dipeptidyl peptidase IV (DPP-IV) inhibitors cause heart failure? *Clin Ther* **36**: 2072–9

Holman RR, Paul SK, Bethel MA et al (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* **359**: 1577–89

Nissen SE, Wolski K (2007) Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* **356**: 2457–71 [Erratum, *N Engl J Med* **357**: 100]

Scirica BM, Bhatt DL, Braunwald E et al (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* **369**: 1317–26

Udell JA, Cavender MA, Bhatt DL et al (2015) Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol* **3**: 356–66

White WB, Cannon CP, Heller SR et al (2013) Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* **369**: 1327–35