**Type 2 diabetes: use of sitagliptin in people with concurrent heart failure**

A US observational study found that use of sitagliptin in people with type 2 diabetes and heart failure was not associated with an increase in all-cause mortality, all-cause hospital admission, or heart failure-related hospital admission or death. However, sitagliptin use was associated with an increased risk of heart failure-related hospital admission alone (number needed to harm 29). Limitations of the study prevent firm conclusions being drawn about sitagliptin, and further evidence is awaited to clarify the cardiovascular safety profile of sitagliptin and other gliptins. Healthcare professionals should continue to follow the NICE clinical guidelines on type 2 diabetes (currently being updated; publication expected August 2015) and chronic heart failure.

**Overview and current advice**

People with type 2 diabetes are at increased risk of developing macrovascular and microvascular complications, namely, cardiovascular and cerebrovascular disease, peripheral vascular disease, neuropathy, renal disease and retinopathy. Mortality is 2 to 3 times higher among people with type 2 diabetes than in the general population, largely due to an increase in cardiovascular mortality. However, there is still uncertainty about which blood glucose-lowering drugs are safe with regards to cardiovascular disease, and which can lower cardiovascular risk.

Heart failure is a frequent complication of type 2 diabetes. Recent studies have attempted to define the risk of cardiovascular complications, including heart failure, associated with dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins). The randomised controlled trial SAVOR-TIMI 53 found that adding saxagliptin to other blood glucose-lowering drugs did not reduce the risk of cardiovascular events in people with type 2 diabetes and a history of, or who were at increased risk of, cardiovascular events. However, saxagliptin was associated with a statistically significantly increased risk of hospitalisation due to heart failure compared with placebo (p=0.007). The Medicines Evidence Commentary: Type 2 diabetes: study finds no benefit from saxagliptin on cardiovascular outcomes reviewed this study, commenting that caution should be exercised when interpreting this individual outcome, especially when the primary outcome of the trial was not statistically significant.
The current NICE clinical guideline on the management of type 2 diabetes recommends a gliptin as an option for dual therapy (with either metformin or a sulfonylurea) or triple therapy (with metformin and a sulfonylurea) within certain criteria. This guideline is being updated (publication expected August 2015) and the recommendations may change.

See the NICE Clinical Knowledge summaries on type 2 diabetes and chronic heart failure for a general overview of these conditions. The NICE Pathways on diabetes and chronic heart failure bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

A US retrospective cohort study with a nested case-control population\(^2\) has evaluated adverse outcomes associated with sitagliptin (the first marketed and most widely used gliptin in the USA) in people with type 2 diabetes and newly diagnosed heart failure.

Using a US insurance claims database, the investigators identified 7620 people aged 20 years or over (mean age 54 years) who were prescribed metformin or a sulfonylurea for type 2 diabetes between 2003 and 2009, and who were subsequently diagnosed with heart failure. Of these, 887 (12%) were prescribed sitagliptin. People who received a glitazone before the heart failure diagnosis were excluded from the study because glitazones are known to be associated with heart failure. The primary outcome was a composite end point of all-cause hospital admission or death. Secondary end points included heart failure-related hospital admission, all-cause hospital admission and all-cause death. Median follow-up was 1.4 years.

A primary outcome event occurred in 4137 subjects (54.3%) in the cohort who were then used as cases in the case-control population. The cases were matched by age and sex to 41,297 controls who had not experienced a primary outcome. Sitagliptin use in the 90 days before the index date (i.e. the time of the event, such as all-cause hospital admission, or pseudo date for matching controls) was compared with no sitagliptin use in this time period, after adjusting for other antidiabetic drugs.

The study found that sitagliptin use was not associated with a statistically significantly increased risk of the primary composite end point. The risk of all-cause hospital admission or death was 7.1% (113/1588) in sitagliptin users and 9.2% (4024/43,846) in non-users (adjusted odds ratio [OR] 0.84; 95% confidence interval [CI] 0.69 to 1.03, \(p=0.10\)). There was also no statistically significant difference between sitagliptin use and non-use in the following secondary outcomes: all-cause death; all-cause hospital admission; or a composite of heart failure-related hospital admission or death. Sitagliptin use was, however, associated with an increased risk of heart failure-related hospital admission alone (12.5% [25/200] in sitagliptin users and 9.0% [799/8862] in non-users, adjusted OR 1.84; 95% CI 1.16 to 2.92, \(p=0.01\)), with a number needed to harm of 29 over 1.4 years.

Commentary provided by the NICE Medicines and Prescribing Centre

This observational study in people with type 2 diabetes and heart failure found that sitagliptin use was not associated with an increased risk of all-cause hospital admission or death, but was associated with an increased risk of heart failure-related hospitalisation alone.
While this new evidence may provide some reassurance when considering the use of gliptins in people with heart failure, there are a number of important factors and limitations that should be taken into account. The observational nature of the study prevents causal inferences being made and further studies are required to fully understand the risk to benefit ratio of sitagliptin, or other gliptins, in people with heart failure. Confounding by indication may have introduced bias because there may be a reluctance to prescribe drugs that may be considered to worsen heart failure in people already at increased risk of the condition. The investigators were unable to control for key factors which affect cardiovascular risk, including body weight and blood pressure. The authors state that people who were prescribed sitagliptin were similar to those not prescribed sitagliptin with respect to most covariates. However, there were differences in history of diabetes complications or ischaemic heart disease before incident heart failure, total cholesterol levels, use of renin-angiotensin drugs and statins that could have affected the findings.

Perhaps most importantly, the number of people prescribed sitagliptin compared with other blood-glucose lowering drugs, such as metformin, was very small and the median duration of follow-up was just 1.4 years. This resulted in very few events, particularly those that were heart-failure specific, in users of sitagliptin, and wide confidence intervals around the risk estimates.

A large randomised controlled trial evaluating cardiovascular outcomes with sitagliptin is currently underway (TECOS), with results expected in 2015. This trial may help to clarify the cardiovascular safety profile of sitagliptin.

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### References


### About this Medicines Evidence Commentary

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