Type 2 diabetes: study finds no benefit from saxagliptin on cardiovascular outcomes

A large randomised controlled trial has found that adding saxagliptin to other blood-glucose-lowering medication did not reduce the risk of cardiovascular events or some renal outcomes at around 2 years. However, saxagliptin increased the risk of hypoglycaemia and may also have increased the risk of admission to hospital because of heart failure. Practitioners should follow NICE guidance on the management of blood glucose and other cardiovascular risk factors in people with type 2 diabetes.

Overview and current advice

The NICE clinical guideline on type 2 diabetes, which is being updated, states that the management of type 2 diabetes is complex. It involves an individualised, multifactorial approach that addresses blood pressure, blood lipids and lifestyle issues, as well as blood glucose. The clinical guideline recommends that people should be involved in setting their individualised HbA1c target level, which may be above the general target of 48 mmol/mol (6.5%), and that pursuing highly intensive management to HbA1c levels below 48 mmol/mol (6.5%) should be avoided.

The NICE MPC type 2 diabetes key therapeutic topic summarises the evidence relating to blood glucose control and vascular outcomes in type 2 diabetes. This suggests that there is a small absolute benefit of intensive compared with conventional blood glucose control in reducing coronary heart disease but no effect on the risk of stroke or death from cardiovascular causes, or the total rate of death. Moreover, an emerging body of evidence suggests that the benefit from intensive blood glucose control is not as great as the benefits from blood pressure control or lipid lowering. There appears to be a reduction in certain microvascular endpoints with intensive compared with conventional blood glucose control, but in studies some of these endpoints were disease-oriented, surrogate outcomes rather than patient-oriented, clinical outcomes (see the Medicines Evidence
Commentary Type 2 diabetes: does intensive blood glucose control improve renal outcomes? for details). Any possible microvascular benefits of intensive blood glucose control need to be balanced against the increased risk of severe hypoglycaemia.

Although newer glucose-lowering drugs are effective at reducing HbA1c levels, they have all lacked robust clinical outcome data, particularly around their cardiovascular effects and long-term safety in people with type 2 diabetes. Improvements in surrogate markers (including HbA1c levels) do not automatically confer benefits on mortality or morbidity, and risks may become apparent only over time when these agents have more widespread use in a diverse population.

NICE has not published guidance relating specifically to saxagliptin, but the NICE clinical guideline on type 2 diabetes recommends considering sitagliptin or vildagliptin, which are also DPP-4 inhibitors, for dual therapy with metformin or a sulfonylurea when 1 of these 2 is contraindicated, not tolerated, or (in the case of sulfonylureas) there is a significant risk of hypoglycaemia. Sitagliptin can also be considered for triple therapy with metformin and a sulfonylurea if insulin is unacceptable or inappropriate. NICE recommends that sitagliptin or vildagliptin should be continued only if the person shows a reduction in HbA1c of at least 5.5 mmol/mol (0.5%) after 6 months. Saxagliptin is included in the scope for the update of the clinical guideline.

See the Clinical Knowledge Summary on type 2 diabetes for a general overview of the condition and prescribing considerations. The NICE Pathway: diabetes brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

A large randomised controlled trial (RCT) – the SAVOR–TIMI 53 study – has assessed the effects of saxagliptin on cardiovascular outcomes in 16,492 people with type 2 diabetes1. Study participants (mean age 65 years) had a history of type 2 diabetes (median 10.3 years) and were either at least 40 years old with established cardiovascular disease (73%), or were at least 55 years old (men) or 60 years old (women) and a current smoker or had dyslipidaemia or hypertension. People with end-stage renal disease were excluded. At baseline the mean HbA1c was 8.0% (approximately 64 mmol/mol) and 73% had an HbA1c 7.0% (approximately 53 mmol/mol) or greater; 22% had an HbA1c greater than 9.0% (approximately 75 mmol/mol). Most patients (70%) were receiving metformin, 40% were receiving a sulfonylurea, 6% were receiving a glitazone and 41% were receiving insulin. Only 4% were receiving no antidiabetic medication. In addition, 75% were receiving aspirin, 78% were receiving a statin, 54% were receiving an ACE inhibitor and 28% were receiving an angiotensin receptor blocker.

Patients were randomised to receive saxagliptin 5 mg daily (or 2.5 mg daily in patients with GFR of 50 ml/min or less) or placebo. Allocation was concealed. All other therapy for the management of the patient’s diabetes and cardiovascular disease – including adding, discontinuing, or changing the dose of concomitant glucose-lowering drugs – was at the discretion of the responsible physician. Concomitant use of other gliptins or glucagon-like peptide 1 agonists was not permitted. The median follow-up period was 2.1 years and the maximum follow-up time was 2.9 years. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischaemic stroke. The secondary efficacy end points included the primary composite end point plus hospitalisation for heart failure, coronary revascularisation, or unstable angina.
The study was designed to test the superiority of saxagliptin for the primary endpoint, with a prespecified initial test for non-inferiority. The criterion for non-inferiority was that the upper 95% confidence interval (CI) for the hazard ratio (HR) of the primary outcome should not exceed 1.3 (that is, non-inferiority was accepted if the 95% CI indicated that the risk of the primary endpoint was not more than 30% greater with saxagliptin than with placebo).

In the intention to treat analysis, the primary endpoint occurred in 7.3% of the saxagliptin group and in 7.2% of the placebo group (according to 2-year Kaplan–Meier estimates; HR 1.00, 95% CI 0.89 to 1.12, p=0.99 for superiority and p<0.001 for non-inferiority). This corresponds to a rate of 3.7 per 100 person-years in both groups. The secondary endpoint occurred in 12.8% of the saxagliptin group and in 12.4% of the placebo group (according to 2-year Kaplan–Meier estimates; HR 1.02, 95% CI 0.94 to 1.11, p=0.66). This corresponds to a rate of 6.6 and 6.5 per 100 person-years, respectively.

The individual components of this outcome showed no statistically significant difference between groups in rates except for the outcome of hospitalisation for heart failure. More patients in the saxagliptin group than in the placebo group were hospitalised for heart failure (3.5% compared with 2.8%, according to 2-year Kaplan–Meier estimates; HR 1.27, 95% CI 1.07 to 1.51; p=0.007). However, caution should be exercised when interpreting such individual components of a composite outcome, especially when the primary outcome of a trial is not statistically significant.

In addition, there was no statistically significant difference in the rate of the composite renal endpoint of doubling of serum creatinine level, initiation of dialysis, renal transplantation, or serum creatinine >530 micromol/l: 2.2% in the saxagliptin group compared with 2.0% in the placebo group, HR 1.08, 95% CI 0.88 to 1.32, p=0.46.

HbA1c levels were statistically significantly lower in the saxagliptin group than in the placebo group throughout the study (7.7% compared with 7.9% at the end of the treatment period [approximately 61 mmol/mol compared with 63 mmol/mol], p<0.001) and more patients in the saxagliptin group than in the placebo group had an HbA1c level of less than 7% by the end of the treatment period (36.2% compared with 27.9%, p<0.001). Fewer patients in the saxagliptin group than in the placebo group required a change in dose of their glucose-lowering medicines or the addition of a new glucose-lowering drug.

More patients in the saxagliptin group than in the placebo group reported at least 1 hypoglycaemic event (15.3% compared with 13.4%, p<0.001). Major hypoglycemic events (requiring intervention of a third party) occurred in 2.1% of patients in the saxagliptin group compared with 1.7% patients in the placebo group (p=0.047). Pancreatitis occurred infrequently, and the same proportion of patients in each group (0.3%) developed acute or chronic pancreatitis (p=0.77). There were 5 cases of pancreatic cancer in the saxagliptin group and 12 in the placebo group (p=0.095).

Commentary

Patients with type 2 diabetes mellitus lose on average 10 years of life, predominantly through accelerated macrovascular disease. Early studies on DPP-4 inhibitors had suggested some degree of cardio-protection. This large trial of saxagliptin therapy, along with others, has failed to show a reduction in macrovascular disease despite demonstrating a significant improvement in glycaemic control. However, a median of two years treatment may have been insufficient time to alter the
underlying atherogenic process in these patients who had diabetes for a median duration of over 10 years. It will be interesting to see longer term cardiovascular outcome data. There was an increased risk of hospitalisation for heart failure during this study. Heart failure has also been noted with other antihyperglycaemic agents in the past; this will therefore need ongoing scrutiny in further studies of DPP-4 inhibitors.

Many patients find hypoglycaemia has a negative impact on their quality of life, and rates of both major and minor hypoglycaemic events were raised over the 2-year study. On a positive note given the publicity over the possible risk of pancreatic cancer with DPP-4 agents, this study showed no excess incidence. However, like macrovascular disease, more than two years may be needed to shed more light on this issue. Reassuringly there was no increased incidence of acute or chronic pancreatitis in those taking saxagliptin.

Saxagliptin is one of the therapeutic options that improve glycaemic control where an HbA1c reduction of 5.5 mmol/mol is likely to bring the patient’s glycaemic control within their personalised target. NICE guidance on the related drugs sitagliptin and vildagliptin position them for use after metformin and sulfonylurea therapy has been initiated or considered, as part of a dual or triple therapy regimen, where insulin is not felt to be appropriate. The update to the NICE clinical guideline will consider the role of saxagliptin. In the meantime, this study showing a lack of evidence of a cardiovascular benefit but providing further reassurance about adverse pancreatic outcomes is unlikely to alter the place of saxagliptin within current clinical practice.

Study sponsorship

This randomised controlled trial was sponsored by AstraZeneca and Bristol-Myers Squibb.

References