Type 2 diabetes: study finds no benefit from alogliptin on cardiovascular outcomes in people with a recent acute coronary syndrome

A large randomised controlled trial has found that adding alogliptin to other blood-glucose-lowering medication did not reduce the risk of cardiovascular events in people with type 2 diabetes who had had a recent acute coronary syndrome, over a median of 18 months. It is expected that alogliptin will be launched in the UK within the next few months. 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 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 from 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, hitherto 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. A clinical trial of the DPP-4 inhibitor saxagliptin was published in October 2013: this 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. This study is discussed further in the NICE Medicines Evidence Commentary Type 2 diabetes: study finds no benefit from saxagliptin on cardiovascular outcomes.

Alogliptin is not currently available in the UK but in July 2013 it received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency. An evidence summary: new medicine on alogliptin was published by the NICE Medicines and Prescribing Centre in May 2013. NICE has not published guidance relating specifically to alogliptin, 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. At present, alogliptin is not included in the scope for the update of the clinical guideline, because it was not anticipated that the licence would be granted in time for inclusion within it.

See the Clinical Knowledge Summary on type 2 diabetes for a general overview of the condition and prescribing considerations. The NICE Pathway: diabetes and the NICE Pathway: hyperglycaemia in acute coronary syndromes bring together all related NICE guidance and associated products on these conditions in a series of interactive topic-based diagrams.

New evidence

A large randomised controlled trial (RCT) – the EXAMINE study – has assessed the effects of alogliptin on cardiovascular outcomes in 5380 people with type 2 diabetes. Study participants (median age 61 years) had a history of type 2 diabetes (median duration 7 years) and had had an acute coronary syndrome within 15 to 90 days before randomisation. Patients were eligible for inclusion if their HbA1c was between 6.5% and 11.0% (7.0% and 11.0% if their treatment included insulin), and the median HbA1c was 8.0%. Patients with unstable cardiac disorders (such as New York Heart Association class IV heart failure and uncontrolled arrhythmias) were excluded.

Patients were randomised to receive alogliptin 25 mg daily (or lower doses in people with estimated glomerular filtration rate [eGFR] of less than 60 ml/min/1.73m²) or placebo. Allocation was concealed. Other treatments for diabetes and cardiovascular risk factors followed local guidelines. At baseline, 30% of patients were receiving insulin, 66% were taking metformin and 47% were taking sulfonylureas. In addition, 91% of patients were taking aspirin, 90% were taking statins and 82% were taking renin-angiotensin system drugs. The median follow-up period was 18 months and the maximum follow-up time was 40 months. The primary endpoint was a composite of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. The secondary endpoint included the primary
The study was designed to test the non-inferiority of alogliptin compared to placebo. The criterion for non-inferiority was that the upper boundary of the 95% confidence interval (CI) for the hazard ratio (HR) of the primary endpoint should not exceed 1.3 (that is, non-inferiority was accepted if the 95% CI indicated that the risk of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke was not more than 30% greater with alogliptin than with placebo). In the intention to treat analysis, the primary endpoint occurred in 11.3% of the alogliptin group and in 11.8% of the placebo group; HR 0.96, upper boundary of the 95% CI ≤1.16, lower boundary not stated, p<0.0001 for non-inferiority, p=0.32 (not statistically significant) for superiority. The secondary endpoint occurred in 12.7% of the alogliptin group and in 13.4% of the placebo group (HR 0.95, upper boundary of the 95% CI ≤1.14, lower boundary not stated, p=0.26 for superiority [not statistically significant]). The individual outcomes of death from any cause and death from cardiovascular causes also showed no statistically significant difference between groups (HR 0.88, 95% CI 0.71 to 1.09, p=0.23; and HR 0.85, 95% CI 0.66 to 1.10, p=0.21 respectively).

HbA1c levels were statistically significantly lower in the alogliptin group than in the placebo group; the least squares mean difference at the end of the study period was −0.36 percentage points (95% CI −0.43 to −0.28, p<0.001).

There were no statistically significant differences between the groups in the rates of adverse events, including any hypoglycaemia (6.5% in the placebo group and 6.7% in the alogliptin group, p=0.74), acute pancreatitis (0.3% and 0.4% respectively, p=0.50) or chronic pancreatitis (0.1% and 0.2% respectively, p=1.00).

Commentary provided by Prof Roger Gadsby MBE, GP and Associate Clinical Professor, Warwick Medical School, University of Warwick and a member of the advisory board of the Institute of Diabetes in Older People (IDOP) University of Bedfordshire

From the manufacturer’s point of view, this trial delivered exactly what it was designed to do, that is demonstrate non inferiority to placebo for cardiovascular disease (CVD) ischaemic events. This is what the Food and Drug Administration (FDA) in the USA said all the companies launching new glucose-lowering therapies have to demonstrate, following the withdrawing of rosiglitazone when evidence that it may increase ischaemic cardiovascular events came to light. This alogliptin trial has been criticised for not demonstrating superiority over placebo, but in my opinion reducing HbA1c by a relatively small amount over a median of 18 months in a group of people with type 2 diabetes who have relatively good glycaemic control, as demonstrated in this study, is hardly likely to reduce CVD ischaemic events significantly, even though they were at high risk of such events. Nevertheless, we must remember that the reason for adding further glucose-lowering drug therapy once blood glucose levels are controlled at reasonable levels is to reduce the risk of macrovascular and microvascular events (the latter not assessed in this study). Prescribers and patients will need to bear the absence of benefit in mind when making decisions about treatment.
The study reassuringly shows no increased risk of pancreatitis or cancer, which have been of concern for incretin-based therapies, although the trial was of relatively short duration and, like macrovascular disease, more than two years may be needed to shed more light on this issue.

Alogliptin is soon to be launched into the UK market, where it will be the fifth agent in the class of DPP-4 inhibitors. It will be interesting to see what effect this evidence has upon prescribers, as some commentators have suggested that incretin-based therapies ought to be prescribed with caution until their cardiovascular safety is confirmed.

Study sponsorship

This randomised controlled trial was sponsored by Takeda

References


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