Type 2 diabetes: study finds empagliflozin reduces adverse cardiovascular outcomes

A large randomised controlled trial has found that adding empagliflozin to standard care in people with type 2 diabetes and established cardiovascular disease reduced the risk of cardiovascular outcomes. The composite end point of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke was reduced with a number needed to treat of 63 over 3 years. However, this was driven by a reduction in the risk of cardiovascular death, not myocardial infarction or stroke. Empagliflozin is a new drug under additional monitoring through the black triangle scheme, and the MHRA has recently warned about the risk of diabetic ketoacidosis with canagliflozin, dapagliflozin and empagliflozin. Clinicians should continue to follow MHRA advice and NICE technology appraisal guidance on empagliflozin. NICE guidelines on type 2 diabetes are currently being updated.

Overview and current advice

The NICE guideline on type 2 diabetes, which is currently being updated (publication date to be confirmed), 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; and recommends that people should be involved in setting their individualised HbA1c target level.

A Cochrane review which compared intensive glycaemic control with conventional glycaemic control found that intensive control did not reduce the risk of death from any cause, cardiovascular death, nonfatal stroke, or cardiac or peripheral revascularisation. However, it did reduce the risk of nonfatal myocardial infarction (MI), amputation of a lower extremity, and microvascular complications (including nephropathy and retinopathy). Intensive glycaemic control also increased the risk of severe adverse events and hypoglycaemia. Therefore any possible benefits need to be balanced against the increased risk of adverse events, particularly hypoglycaemia.

Although all blood glucose-lowering drugs are effective in reducing HbA1c levels, clinical outcome data, particularly around cardiovascular outcomes, are limited. Metformin, sulfonylureas and insulin have outcome data from the UKPDS study. In the original UKPDS study, intensive glycaemic control with sulfonylureas or insulin compared with conventional control (median HbA1c after 10 years follow up 7.0% versus 7.9%) reduced the risk of microvascular complications, but not macrovascular
disease. In people who were overweight or obese, intensive glycaemic control with metformin compared with conventional control (median HbA1c after 10.7 years follow up 7.4% versus 8.0%) reduced the risk of MI and death from any cause. Long-term follow-up of the UKPDS study found a continued reduction in microvascular risk and emergent risk reductions for MI and death in the sulfonylurea-insulin group and a continued benefit for risk of MI and death in the metformin group.

Other blood glucose-lowering drugs have not shown such cardiovascular benefits in people with type 2 diabetes. For example, in PROACTIVE, pioglitazone did not reduce the composite primary end point of death from any cause, nonfatal MI, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation in people with type 2 diabetes and pre-existing major macrovascular disease, but did increase the incidence of oedema, weight gain and heart failure. In SAVOR-TIMI 53, saxagliptin did not reduce the composite primary end point of cardiovascular death, MI, or ischemic stroke, but did increase the risk of admission to hospital because of heart failure in people with type 2 diabetes who had established cardiovascular disease, or were current smokers, or had dyslipidaemia or hypertension. In EXAMINE, alogliptin did not reduce the composite primary end point of death from cardiovascular causes, nonfatal MI or nonfatal stroke in people with type 2 diabetes who had had a recent acute coronary syndrome. Similarly, in TECOS, sitagliptin did not reduce the composite primary end point of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospital admission for unstable angina in people with type 2 diabetes who had established cardiovascular disease.

A cardiovascular outcome study (EMPA-REG OUTCOME) of the sodium glucose cotransporter 2 (SGLT-2) inhibitor empagliflozin has now been published. NICE technology appraisal guidance for empagliflozin in combination therapy for treating type 2 diabetes states:

- Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:
  - a sulfonylurea is contraindicated or not tolerated, or
  - the person is at significant risk of hypoglycaemia or its consequences.
- Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:
  - metformin and a sulfonylurea or
  - metformin and a thiazolidinedione (pioglitazone).
- Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.
- People currently receiving treatment initiated within the NHS with empagliflozin that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

NICE technology appraisal guidance for the other licensed SGLT-2 inhibitors canagliflozin and dapagliflozin also recommends these medicines as options for combination therapy in specified circumstances (see the guidance for details). A multiple technology appraisal on canagliflozin, dapagliflozin and empagliflozin for the monotherapy treatment of type 2 diabetes is in progress (publication expected May 2016).

Empagliflozin and the other SGLT-2 inhibitors are new medicines that are under additional monitoring through the black triangle scheme. In the June 2015 edition of Drug Safety Update, the MHRA warned about the risk of diabetic ketoacidosis (DKA) with canagliflozin, dapagliflozin and empagliflozin. Serious and life-threatening cases of DKA have been reported in people taking SGLT-2 inhibitors and, in several cases, blood glucose levels were only moderately elevated, which is atypical for DKA. When treating people who are taking an SGLT-2 inhibitor the MHRA recommends the following:

- test for raised ketones in people with symptoms of DKA; omitting this test could delay diagnosis of DKA
- if you suspect DKA, stop SGLT-2 inhibitor treatment
- if DKA is confirmed, take appropriate measures to correct the DKA and to monitor glucose levels
- inform people of the symptoms and signs of DKA; advise them to get immediate medical help if these occur
- be aware that SGLT-2 inhibitors are not approved for treatment of type 1 diabetes
- continue to report suspected side effects to SGLT-2 inhibitors on a Yellow Card.
The FDA has also recently revised the canagliflozin label to include updates on bone fracture risk and new information on decreased bone mineral density.

New evidence

A large randomised controlled trial – EMPA-REG OUTCOME – has assessed the effects of empagliflozin or placebo, in addition to standard care, on cardiovascular morbidity and mortality in 7020 people with type 2 diabetes. Study participants (median age 63 years, 71% male, mean body mass index 31 kg/m²) had a history of type 2 diabetes and had established cardiovascular disease (history of MI, stroke or coronary artery or occlusive peripheral artery disease). Participants were eligible for inclusion if their HbA1c was 7.0%–9.0% if they had received no glucose-lowering drugs for at least 12 weeks before randomisation or 7.0%–10.0% if they had received stable glucose-lowering therapy for at least 12 weeks before randomisation. The median HbA1c level at baseline was 8.1%. People with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m² were excluded.

Participants were randomised 1:1:1 to receive empagliflozin 10 mg (n=2345), empagliflozin 25 mg (n=2342) or placebo (n=2333) once daily. Randomisation was stratified according to various criteria and allocation was concealed. Other treatments for diabetes and cardiovascular risk factors followed local guidelines. However, for the first 12 weeks, glucose-lowering treatment was to remain unchanged. At baseline, 74% of participants were taking metformin, 48% were receiving insulin, 43% were taking sulfonylureas, 11% were taking dipeptidyl peptidase-4 (DPP-4) inhibitors, 4% were taking thiazolidinediones and 3% were taking glucagon-like peptide-1 (GLP-1) mimetics. In addition, 83% of participants were taking aspirin, 81% were taking lipid-lowering drugs (mean LDL-cholesterol 2 mmol/L) and 95% were taking blood pressure-lowering drugs (mean blood pressure 136/77 mmHg). The median follow-up period was 3.1 years. The primary end point was a composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke. The key secondary end point included the primary end point plus hospital admission for unstable angina.

The study was designed to test the non-inferiority of empagliflozin (pooled doses of 10 mg and 25 mg daily) compared with 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 end point should not exceed 1.3 (that is, non-inferiority was accepted if the 95% CI indicated that the risk of the primary end point was not more than 30% greater with empagliflozin than with placebo). If non-inferiority was shown, superiority could be tested for.

In the modified intention to treat population (participants who had received at least 1 dose of study drug), the primary end point occurred in 10.5% of the pooled empagliflozin group and in 12.1% of the placebo group; hazard ratio (HR) 0.86; 95% confidence interval (CI) 0.74 to 0.99. This was statistically significant for non-inferiority (p=0.001) and for superiority (p=0.04). The key secondary end point occurred in 12.8% of the pooled empagliflozin group and in 14.3% of the placebo group; HR 0.89; 95% CI 0.78 to 1.01. This was statistically significant for non-inferiority (<0.001) but not superiority (p=0.08). The individual outcomes of death from any cause, death from cardiovascular causes and hospital admission for heart failure were also statistically significantly reduced with empagliflozin (HR 0.68, 95% CI 0.57 to 0.82, p=0.001; HR 0.62, 95% CI 0.49 to 0.77, p<0.001 and HR 0.65, 95% CI 0.50 to 0.85, p=0.002 respectively). However, there were no statistically significant reductions in MI, stroke or hospital admission for unstable angina. There was no difference between the 10 mg empagliflozin dose and the 25 mg empagliflozin dose with respect to cardiovascular outcomes.

The numbers needed to treat with empagliflozin over 3 years were 63 to prevent 1 primary end point (death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke), 39 to prevent 1 death from any cause, 46 to prevent 1 cardiovascular death and 72 to prevent 1 hospital admission for heart failure in this population of people with type 2 diabetes and established cardiovascular disease.

At 12 weeks, during which glucose-lowering treatment was to remain unchanged, the adjusted mean differences in HbA1c levels between participants receiving empagliflozin and those receiving placebo were −0.54 percentage points in the 10 mg group and −0.60 percentage points in the 25 mg group. At week 206 these differences had reduced to −0.24 percentage points in the 10 mg group and −0.36 percentage points in the 25 mg group. The adjusted mean HbA1c levels at week 206 were
7.81% (61.9 mmol/mol) in the pooled empagliflozin group and 8.16% (65.7 mmol/mol) in the placebo group. Over the course of the study, empagliflozin was associated with small reductions in weight and blood pressure, and small increases in LDL- and HDL-cholesterol.

The percentages of participants who had any adverse event (90.2% compared with 91.7%), any severe adverse event (23.5% compared with 25.4%), any adverse event that led to discontinuation (17.3% compared with 19.4%) or any confirmed hypoglycaemic adverse event (27.8% compared with 27.9%) were similar in the pooled empagliflozin group compared with the placebo group. Genital infection was reported in a higher percentage of participants in the pooled empagliflozin group (5.0% compared with 1.5% in male patients and 10.0% compared with 2.6% in female patients). Urosepsis was reported in 0.4% of participants in the pooled empagliflozin group and 0.1% of the placebo group but the overall rates of urinary tract infection (UTI), complicated UTI or pyelonephritis were similar. There were 4 DKA events in the pooled empagliflozin group (n=4687) and 1 in the placebo group (n=2333). Bone fracture occurred in 3.8% of the pooled empagliflozin group and 3.9% of the placebo group.

Commentary

Commentary provided by Dr TA Chowdhury MD, FRCP, Consultant in Diabetes, The Royal London Hospital

The last decade has seen a significant increase in the number of medicines used for treating type 2 diabetes. Whilst all have demonstrable effects on lowering glucose (as outlined above) few have shown genuine cardiovascular benefits. Of all blood glucose-lowering drugs, metformin appears to be the safest, and has shown benefits in preventing cardiovascular morbidity and mortality. There have been longstanding concerns about the cardiovascular effects of glitazones, and possibly sulfonylureas. DPP-4 inhibitors have been tested for cardiovascular safety, and whilst they have shown reassuringly no adverse cardiovascular effects, they have not demonstrated significant cardiovascular benefits in people with type 2 diabetes. There is a view that blood-glucose lowering drugs should demonstrate cardiovascular benefits before being licensed.

It is therefore of interest to see the first cardiovascular outcomes study for the latest class of oral blood glucose-lowering drugs, SGLT-2 inhibitors, showing cardiovascular benefits. The Kaplan Meier plots appear to have separated within 6 months of treatment, suggesting a rapid effect. However, they also diverge markedly between 42 and 48 months when numbers in both groups drop markedly. This was unexplained and may affect the results. The difference in glycaemic control between the empagliflozin groups and the placebo group was modest at around 0.5% to 0.6%, and this difference waned over time. Indeed, median HbA1c was around 7.8% in the empagliflozin group at the end of the trial (from a baseline of 8.1%), suggesting that many had only modest glycaemic control. SGLT-2 inhibitors have been advocated for obese patients due to their positive effects on weight reduction, but disappointingly little weight loss was achieved in this trial. Apart from an increased risk of genitourinary infections, very few excess adverse events were seen with empagliflozin. No increased risk of diabetic ketoacidosis, thromboembolic events or bone fracture was seen, all of which have been suggested as possible concerns with SGLT-2 inhibitors. However, the number of people included in the trial was still relatively low to capture data on rare adverse events, and prescribers should continue to follow the MHRA advice on SGLT-2 inhibitors outlined above.

Management of cardiovascular risk factors (smoking, blood pressure and LDL-cholesterol) are the paramount clinical priorities in treating people with type 2 diabetes. It is welcome, however, that we now have some robust evidence for cardiovascular risk reduction using blood glucose-lowering drugs other than metformin. The people in the trial were already at high cardiovascular risk because they had established cardiovascular disease; hence caution should be applied to extrapolating the findings to a wider population of people with type 2 diabetes. It is noteworthy that the reduction in the composite end point was driven by death from cardiovascular causes, but no reduction in myocardial infarction or stroke was seen. It may be important, therefore, to await further studies of SGLT-2 inhibitors before significantly changing prescribing practice.
Study sponsorship

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References

1. Hemmingsen B, Lund SS, Gluud C et al. (2013) Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD008143. DOI: 10.1002/14651858.CD008143.pub3. This review has been withdrawn because of the involvement of 2 authors being employed in pharmaceutical companies. The authors of the review and the Cochrane Metabolic and Endocrine Disorders Group did not find that this was a breach of the rules of the Cochrane Collaboration at the time when it was published. However, after the publication of the review, the Cochrane Collaboration requested withdrawal of the review due to the employment of the 2 authors. A new protocol for a review to cover this topic will be published. This will have a new title and a markedly improved protocol fulfilling new and important developments and standards within the Cochrane Collaboration as well as an improved inclusion and search strategy making it necessary to embark on a completely new review project.


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