Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation

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Scientific summary

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Scientific summary

The prevalence of type 2 diabetes has been increasing in the UK, and over 3.5 million people in England have the disease. People with type 2 diabetes are at risk of the complications of diabetes, including visual loss, renal failure and neuropathy, and an excess risk of cardiovascular disease (CVD).

Most people with type 2 diabetes are overweight, so treatment starts with lifestyle advice, aimed at reducing weight and increasing physical activity. Even modest amounts of weight loss can improve glycaemic control.

If drug treatment is necessary, the drug of first choice is metformin. However, some people cannot tolerate metformin. It causes troublesome diarrhoea in 5–10% of people. It is not used in people with renal impairment.

If drug treatment is required to control high blood glucose levels when metformin cannot be used, the other options include:

- sulfonylureas (SUs)
- pioglitazone
- the dipeptidyl peptidase-4 (DPP-4) inhibitors
- repaglinide.

All are oral medications, licensed for use in monotherapy. The SUs have been used for decades and are available in inexpensive generic forms. Gliclazide costs around £30 a year, or around £60–80 a year for the modified-release form. Their safety record is well known. They can cause weight gain and hypoglycaemia.

Pioglitazone is also available in generic form, costing around £21 a year. It has adverse effects (AEs) of weight gain, oedema, heart failure and fractures. There has been concern over an increased risk of bladder cancer but recent research is reassuring.

The DPP-4 inhibitors, such as sitagliptin (Januvia, Merck Sharp & Dohme Limited, Kenilworth, NJ, USA), are a more recent group, with no generic forms, and cost around £430 a year. They are well tolerated, and do not cause weight increase.

The newest group of drugs are the sodium–glucose co-transporter 2 (SGLT2) inhibitors. These inhibit a mechanism in the kidney that conserves glucose by reabsorbing it from the urine. So glucose is lost in the urine, which reduces the blood glucose level and also leads to a loss of calories, which leads to weight loss. They have a mild diuretic effect and a modest blood pressure (BP)-lowering effect. They cost around £470 a year.

This report reviews the clinical effectiveness and cost-effectiveness of three SGLT2 inhibitors – dapagliflozin (Farxiga, Bristol-Myers Squibb, Luton, UK), canagliflozin (Invokana, Janssen, High Wycombe, UK) and empagliflozin (Jardiance, Boehringer Ingelheim, Ingelheim, Germany/Eli Lilly and Company, Indianapolis, IN, USA) – in monotherapy in people who cannot take metformin.

Methods

We searched MEDLINE and EMBASE for randomised controlled trials lasting 24 weeks or more. The trials were then critically appraised and summarised. For adverse events, a wider range of studies was used. A network meta-analysis (NMA) was carried out involving the three SGLT2 inhibitors and key comparators. Cost-effectiveness modelling was done using the United Kingdom Prospective Diabetes Study (UKPDS) outcome model, version 1.

Results

Seven trials were obtained, three of dapagliflozin and two each for canagliflozin and empagliflozin. All were of good quality. The canagliflozin and dapagliflozin trials compared them with placebo, but the two empagliflozin trials included active comparators, one sitagliptin and one linagliptin (Trajenta, Boehringer Ingelheim, Bracknell, UK). All three drugs were effective in improving glycaemic control, promoting weight loss and lowering BP. The main outcome was glycaemic control as reflected in reductions in glycated haemoglobin (HbA_{1c}), where a reduction of 0.5% or more is regarded as clinically useful.

In the three trials of dapagliflozin 10 mg daily, HbA_{1c} was reduced by 0.39%, 0.66% and 0.82% more than on placebo. The trial with the smallest reduction had the lowest baseline HbA_{1c} of 7.5%. Generally speaking, the higher the baseline HbA_{1c} in trials, the greater the reduction seen. Patients lost between 1.1 kg and 2 kg more than in the placebo groups, though it is worth noting that two trials were carried out in China and Japan where starting body mass indices (BMIs) were around 26 kg/m^2. The placebo groups lost between 0.27 kg and 2.2 kg, and improved HbA_{1c} (by 0.23%, 0.29% and 0.06%). Systolic blood pressure (SBP) fell by 2.7 to 3.1 mmHg.

One canagliflozin trial was carried out in Japan and the other in 17 countries. On canagliflozin 100 mg daily, HbA_{1c} was reduced in the two trials by 0.91% and 1.01% more than on placebo, from baselines of 8.0%. One trial also used a dose of 300 mg, which reduced HbA_{1c} by 1.17%. On 100 mg daily, weight loss was around 2 kg, and SBP was reduced by 3.7 and 5.2 mmHg. On 300 mg daily, weight loss was 2.9 kg. In both the canagliflozin trials, the placebo group HbA_{1c} rose (by 0.14% and 0.29%).

One trial compared empagliflozin with linagliptin in 197 centres in 22 countries. The other compared empagliflozin with placebo and sitagliptin in 124 centres in nine countries, mainly Western countries but including China, India and Japan. Compared with placebo, empagliflozin 10 mg reduced HbA_{1c} by 0.74% and empagliflozin 25 mg by 0.86%. Weight loss was about 2 kg, and SBP was reduced by 2.6 and 3.4 mmHg.

The only significant AEs reported in the seven trials were increases in urinary and genital tract infections (GTIs), mainly in women, in about 4% to 9%.

Long-term cardiovascular outcome studies are being carried out on all three drugs, but the only one to report is the empagliflozin outcomes trial. All-cause mortality at a median of 3 years was 8.3% in the placebo group and 5.7% in the pooled empagliflozin group. This was mainly due to differences in cardiovascular deaths – 5.9% and 3.7%. The difference in cardiovascular mortality was mainly due to sudden death (1.6% and 1.1%), heart failure (0.8% and 0.2%) and an ill-defined category of 'other cardiovascular deaths' (2.4% and 1.6%). However, nearly all patients were on combination diabetes therapy. Half were on insulin-containing regimens. They are not comparable with patients being considered for monotherapy. They were selected as being at very high risk of CVD.

Network meta-analysis

We included the three SGLT2 inhibitors, pioglitazone, gliclazide, sitagliptin, vildagliptin (Galvus, Novartis Frimley, UK) and linagliptin in a NMA using placebo as a common comparator as far as possible. Compared with placebo, reductions in HbA_{1c} were:

- canagliflozin 300 mg: 1.19%
- canagliflozin 100 mg: 0.95%
- empagliflozin 25 mg: 0.88%
- empagliflozin 10 mg: 0.76%
- dapagliflozin 10 mg: 0.59%.

A caveat is necessary regarding the effects of the larger doses of canagliflozin and empagliflozin, which is that, according to the licences, the larger doses should only be used in people who have tolerated the starting doses but have had an insufficient response. Those who do not respond well to the starting dose might not achieve the same effects as did people in the trials randomised to the larger dose from the start.

In considering the smaller effect size with dapagliflozin 10 mg, the improvements in the placebo groups in the dapagliflozin trials should be noted, in contrast to the canagliflozin trials where HbA_{1c} rose in the placebo groups.

The reductions in HbA_{1c} with pioglitazone, gliclazide and sitagliptin were 1.13%, 0.95% and 0.76%, respectively.

Another caveat is that some trials recruit patients with quite high HbA_{1c} levels, and the reductions seen in HbA_{1c} may be much larger than would be seen in patients managed according to National Institute for Health and Care Excellence (NICE) guidelines with frequent monitoring and prompt intensification once their HbA_{1c} exceeded 7.5%.

Cost-effectiveness: manufacturer modelling

Janssen, AstraZeneca and Boehringer Ingelheim submitted cost-effectiveness modelling exercises.

All the company submissions applied an annual cost of £608 for canagliflozin 300 mg, being submitted before the price reduction in August 2015 to the same £477 annual price for canagliflozin 100 mg. So the summary of cost-effectiveness results of the companies concentrates upon the canagliflozin 100 mg results.

Janssen used the Economic and Health Outcomes Model for Type 2 Diabetes Mellitus (ECHO-T2DM) model. AstraZeneca, Boehringer Ingelheim and the Assessment Group (AG) used models based upon either the UKPDS68 or upon a combination of the UKPDS68 and the UKPDS82.

The Janssen model assumed that after an initial treatment effect HbA_{1c} would increase at a constant rate. This rate was treatment specific. The annual rate of increase in HbA_{1c} associated with a treatment could be as important as the initial treatment effect upon HbA_{1c}.

Janssen estimated that pioglitazone has the lowest total lifetime costs of £20,264 and yields an average 9.998 quality-adjusted life-years (QALYs). Gliclazide was estimated to be somewhat more expensive than pioglitazone, with total costs of £20,956 and to yield 9.949 QALYs, so is dominated by pioglitazone. Sitagliptin was also more expensive, with a total cost of £23,442 and to yield a total of 9.981 per QALY, so was dominated by pioglitazone, though has a cost-effectiveness estimate compared with gliclazide of £6969 per QALY.

Janssen estimated that canagliflozin 100 mg has total costs of £23,525 and yields 10.039 QALYs, which implies a cost-effectiveness estimate of £79,537 per QALY compared with pioglitazone. The cost-effectiveness estimate compared with gliclazide was £3377 per QALY, this being largely due to the higher costs in the gliclazide arm (using the modified-release form) compared with pioglitazone. Canagliflozin 100 mg was estimated to dominate empagliflozin 10 mg, empagliflozin 25 mg and dapagliflozin 10 mg.

The Janssen cost-effectiveness estimates for the flozins compared with sitagliptin were £1414 per QALY for canagliflozin 100 mg, £1977 per QALY for empagliflozin 25 mg, £4724 per QALY for empagliflozin 10 mg and £6040 per QALY for sitagliptin.

The AstraZeneca submission used the Cardiff Diabetes Model (CDM), which has been revised to use the equations of UKPDS68 to evolve the risk factors and the equations of UKPDS82 to calculate the probabilities of events and death.

AstraZeneca pooled the flozins into a class effect. Given this, pioglitazone was estimated to be the least costly with total costs of £26,067 and to yield 13.111 QALYs. The SUs were estimated to have a total cost of £26,582, so £515 higher than pioglitazone, and to yield 13.179 QALYs, so have a cost-effectiveness estimate of £7574 per QALY compared with pioglitazone. The gliptins were estimated to have a total cost of £27,873 and to yield 13.188 QALYs or only 0.009 QALYs more than the SUs, hence have a cost-effectiveness compared with the SUs of £143,000 per QALY. The flozins were only £106 more expensive than the gliptins and yielded an additional 0.018 QALYs, so had a cost-effectiveness compared with the gliptins of £5904 per QALY. But the flozins cost-effectiveness compared with the SUs was poor at £52,047 per QALY.

AstraZeneca sensitivity analyses showed that results were sensitive to the HbA_{1c} intensification threshold and the assumptions around the evolution of weight.

The Boehringer Ingelheim submission built a visual basic front and back end to the UKPDS Outcomes Model v1 (OM1) model. The OM1 model uses the UKPDS68 equations for the evolution of the risk factors and the calculation of the probability of events.

Some Boehringer Ingelheim figures were classed as confidential, so are not reported in this monograph. The Boehringer Ingelheim modelling estimated that pioglitazone was the least expensive treatment. Only repaglinide was close to being cost-effective compared with pioglitazone, with a cost-effectiveness estimate of £25,349 per QALY. Boehringer Ingelheim included costs (£52.64) of self-monitoring of blood glucose (SMBG) for both repaglinide and pioglitazone, whereas it would be unnecessary with pioglitazone. Empagliflozin 25 mg and empagliflozin 10 mg were estimated to be more expensive than pioglitazone but to yield additional QALYs, giving cost-effectiveness estimates of £46,480 per QALY and £50,892 per QALY compared with pioglitazone. The cost-effectiveness estimates for empagliflozin 25 mg and 10 mg compared with sitagliptin were somewhat better, resulting in cost-effectiveness estimates of around £7333 per QALY and £8325 per QALY, respectively.

Cost-effectiveness: assessment group modelling

The AG modelling suggests that gliclazide is the least expensive, with total costs of £27,314. Repaglinide and pioglitazone have similar total costs of £27,413 and £27,543, respectively. The increased costs for pioglitazone are due in part to the AG including annual brain natriuretic peptide monitoring, which is not standard practice. Costs increase quite markedly with sitagliptin at a total cost of £32,358, and increase further with the flozins being clustered between £32,676 and £32,866. Sitagliptin is estimated to be £5045 more expensive than gliclazide, and the flozins between £5362 and £5553 more expensive than gliclazide.

If there are no direct quality-of-life (QoL) impacts from weight changes, gliclazide is estimated to yield 10.392 QALYs. This is the highest total QALYs for this BMI scenario and, as a consequence, gliclazide dominates all the other treatments.

Including direct QoL impacts from weight changes, and assuming that the weight changes associated with the monotherapies persist indefinitely, results in repaglinide now being superior to gliclazide by 0.030 QALYs and so having a cost-effectiveness estimate of £3331 per QALY. Repaglinide formally dominates pioglitazone and sitagliptin, but canagliflozin yields an additional 0.177 QALYs at an additional cost of £5262, so has a cost-effectiveness estimate of £44,994 per QALY compared with repaglinide. If weight losses associated with treatment tend to rebound at either 1 year or at treatment intensification, the cost-effectiveness estimate for canagliflozin compared with repaglinide worsens to £192,000 per QALY and £119,000 per QALY, respectively.

Over a lifetime, canagliflozin is estimated to be around £100 less expensive than empagliflozin and £200 less expensive than dapagliflozin. With no direct QoL effects from weight changes, it is estimated to be marginally more effective by 0.002 QALYs than empagliflozin and more effective by 0.013 QALYs than dapagliflozin. Including the effects of weight upon QoL increases these net gains to 0.034 QALYs and 0.046 QALYs if weight changes persist indefinitely. If they rebound after 1 year then these gains fall to 0.007 QALYs and 0.019 QALYs, whereas if they rebound at treatment change they fall to 0.014 QALYs and 0.026 QALYs.

These very small differences in QALY gains lead to incremental cost-effectiveness ratio (ICERs) that can vary widely.

Both canagliflozin and empagliflozin have reasonable cost-effectiveness estimates compared with sitagliptin of £12,623 per QALY and £18,341 per QALY, even if there are no QoL impacts from weight changes. Including these effects improves their cost-effectiveness estimates compared with sitagliptin.

Dapagliflozin fares slightly worse compared with sitagliptin. It costs an additional £508, but yields only an additional 0.013 QALYs if there are no direct QoL impacts from weight changes, so has a cost-effectiveness estimate of £40,383 per QALY compared with sitagliptin. This improves to £6632 per QALY if weight changes have a QoL impact and are assumed to persist indefinitely.

The base case applied the baseline HbA_{1c} of 8.4% values for those starting monotherapy from the NICE clinical guideline. This differs from some of the companies' modelling, which assumed a common baseline HbA_{1c} of 7.5%. As would be expected, this both improved patient outcomes and lowered total costs. It did not alter the patterns of dominance.

Of more interest was that the cost-effectiveness estimates of the flozins compared with sitagliptin worsened. With no direct QoL impacts from weight, these worsened to £24,939 per QALY for canagliflozin, £30,150 per QALY for empagliflozin and £54,863 per QALY for dapagliflozin. If the monotherapy BMI effects persist for the patient lifetime then these cost-effectiveness estimates improve to £3717 per QALY, £6042 per QALY and £7442 per QALY, respectively. Weight loss rebound after 1 year reduces the improvements to £14,961 per QALY, £21,643 per QALY and £38,256 per QALY.

Making the HbA_{1c} treatment effect a function of patients' baseline HbA_{1c} had little practical impact upon the cost-effectiveness estimates for the flozins compared with gliclazide, repaglinide and pioglitazone. But it improved the cost-effectiveness estimates for canagliflozin compared with sitagliptin by around one-third. The impact for empagliflozin is less, and there was little impact for dapagliflozin. This is as would be expected given the greater HbA_{1c} effect for canagliflozin compared with sitagliptin, the slightly greater effect for empagliflozin and broad equivalence between dapagliflozin and sitagliptin.

Janssen applied linear evolutions of HbA_{1c} with the annual rate of change being treatment specific, and slower on pioglitazone. Applying the same annual rates of change within the AG modelling reduced total costs and increased total QALYs quite considerably. It also caused pioglitazone to be estimated as the cheapest treatment, with it dominating gliclazide.

The linear HbA_{1c} evolutions still saw the flozins dominated unless there were direct QoL impacts from weight changes.

Assuming that adding gliclazide at the first intensification causes only a 0.47% reduction in HbA_{1c} (based on starting it at HbA_{1c} of just over 7.5%) compared with the 1.01% reduction of the base case has little to no impact for gliclazide and repaglinide, as patients will not use this intensification. But it increases costs and reduces QALYs in the other arms, so worsening the cost-effectiveness estimates for the flozins. The cost-effectiveness estimates for the flozins compared with sitagliptin are not particularly affected, though those for dapagliflozin do worsen slightly.

Overall, the flozins are not cost-effective compared with gliclazide, pioglitazone and repaglinide, but can compete with sitagliptin.

The average costs per QALY will apply to the 'average patient' and there will be instances when patients may be more susceptible to AEs. For example, the risks of fracture with pioglitazone will be greater in women with reduced bone density. In some people, especially the elderly, the risks of hypoglycaemia with SUs may be deemed unacceptable. In others, SU or repaglinide use may require SMBG for driving.

Research needs

The main research need is for long-term data on cardiovascular outcomes for canagliflozin and dapagliflozin. Large studies are under way.

Research is also needed in elderly patients, and in those who develop type 2 diabetes at younger ages.

Conclusions

Dapagliflozin, canagliflozin and empagliflozin are effective in reducing hyperglycaemia and improving glycaemic control, with added benefits of some reductions in BP and weight. The only common AEs are increases in urinary and GTIs, but in a small proportion of users. In monotherapy, the three drugs do not appear cost-effective compared with gliclazide, pioglitazone or repaglinide, but may be competitive against sitagliptin.

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