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Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes

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ABSTRACT

Background: Despite the number of medications for type 2 diabetes, many people with the condition do not achieve good glycaemic control. Some existing glucose-lowering agents have adverse effects such as weight gain or hypoglycaemia. Type 2 diabetes tends to be a progressive disease, and most patients require treatment with combinations of glucose-lowering agents. The sodium glucose co-transporter 2 (SGLT2) receptor inhibitors are a new class of glucose-lowering agents.

Objective: To assess the clinical effectiveness and safety of the SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes.

Data sources: MEDLINE, Embase, Cochrane Library (all sections); Science Citation Index; trial registries; conference abstracts; drug regulatory authorities; bibliographies of retrieved papers.

Inclusion criteria: Randomised controlled trials of SGLT2 receptor inhibitors compared with placebo or active comparator in type 2 diabetes in dual or combination therapy.

Methods: Systematic review. Quality assessment used the Cochrane risk of bias score.

Results: Seven trials, published in full, assessed dapagliflozin and one assessed canagliflozin. Trial quality appeared good. Dapagliflozin 10 mg reduced HbA1c by −0.54% (weighted mean differences (WMD), 95% CI −0.67 to −0.40) compared to placebo, but there was no difference compared to glipizide. Canagliflozin reduced HbA1c slightly more than sitagliptin (up to −0.21% vs sitagliptin). Both dapagliflozin and canagliflozin led to weight loss (dapagliflozin WMD −1.81 kg (95% CI −2.04 to −1.57), canagliflozin up to −2.3 kg compared to placebo).

Limitations: Long-term trial extensions suggested that effects were maintained over time. Data on canagliflozin are currently available from only one paper. Costs of the drugs are not known so cost-effectiveness cannot be assessed. More data on safety are needed, with the Food and Drug Administration having concerns about breast and bladder cancers.

Conclusions: Dapagliflozin appears effective in reducing HbA1c and weight in type 2 diabetes, although more safety data are needed.

ARTICLE SUMMARY

Article focus

- The efficacy and safety of sodium glucose co-transporter 2 (SGLT2) inhibitors.

Key messages

- SGLT2 inhibitors are clinically effective in type 2 diabetes for improving glycaemic control.
- They also lead to reductions in weight.
- SGLT2 appear to be safe in the short-term but longer term data are needed.

Strengths and limitations of this study

- Rigorous systematic review by independent group.
- Clearly defined protocol with defined inclusions and exclusions.
- Searches updated July 2012.
- Focus on clinically relevant trials.
- Only two trials against active comparators.
- No trials of use in triple oral therapy.
- No long-term data of SGLT2 safety available.

INTRODUCTION

Type 2 diabetes is one of the most important and prevalent chronic diseases today, with an excess of 2.6 million people affected in the UK in 2010.[1] The guidelines on the management of type 2 diabetes from the UK's National Institute for Clinical Excellence, recommend that if lifestyle intervention is insufficient, the first line of drug treatment is metformin, followed by a sulphonylurea, or sometimes a glitazone, before starting on insulin. However, sulphonylureas, glitazones and insulin all cause weight gain which may worsen insulin resistance. The sulphonylureas and insulin can also cause hypoglycaemia. Pioglitazone, now the only glitazone left in use, can cause oedema, heart failure and fractures.

It is estimated that 65% of people with diabetes will die as a result of cardiovascular complications,[2 3] therefore antidiabetic medications need not only to produce a

reduction in HbA1c, but ideally also a reduction in cardiovascular disease mortality.

Glucose is normally filtered in the kidney and is reabsorbed in the proximal tubules. Glycosuria occurs when the renal threshold of glucose (blood glucose of approximately 10 mmol/l (160–180 mg/dl) has been reached. At this threshold the proximal tubule cannot reabsorb all of the filtered glucose, resulting in glycosuria. In total, 98% of the urinary glucose is transported across the membrane of the proximal tubule by sodium glucose co-transporter 2 (SGLT2). A naturally occurring mutation in the SLC5A2 gene, resulting in a defective SGLT2 protein, produces significant glycosuria. Individuals who have this mutation have not been seen to have significant problems related to the glycosuria, such as urinary tract infections (UTIs).[4]

Therefore a therapeutic option in type 2 diabetics is to mimic the effect of the SLC5A2 mutation and prevent the reabsorption of renal-filtered glucose back into the circulation, thereby reducing hyperglycaemia, without the side effects of weight gain or hypoglycaemia.[5]

A new class of drugs has been developed to do this, and in this systematic review we review the evidence for clinical effectiveness and safety of the new SGLT2 inhibitor drugs (dapagliflozin, formerly known under the synonym: BMS-512148 and canagliflozin (JNJ28431754)). Since there are existing drugs which are inexpensive and with a long safety record, it is unlikely that SGLT2 inhibitors would be used first line, and we therefore review their role as second or third drugs used in combination therapy in type 2 diabetes.

The key questions for this review are:

How does the clinical effectiveness of the SGLT2 inhibitors compare with that of current pharmacological interventions, when prescribed in dual therapy, for example, metformin plus SGLT2 vs metformin plus sulphonylurea, and in triple therapy, for example, metformin, sulphonylurea and SGLT2 inhibitor versus metformin, sulphonylurea and dipeptidyl peptidase 4 inhibitors (DPP4) such as sitagliptin.

We also considered trials of SGLT2 inhibitors against placebo in dual and triple therapies.

METHODS

The review of the evidence for clinical effectiveness was undertaken systematically, following the general principles recommended in the Cochrane Handbook for Systematic Reviews of Intervention.[6]

Eligibility criteria

Study design

Randomised controlled trials (RCT) and systematic reviews of trials were used for assessing efficacy. As HbA1c is the main outcome being measured, no trial covering less than 8 weeks was accepted into the review, due to that being the minimum period required for a measureable change in HbA1c levels to be detected due to turnover of red blood cells.

Quality-of-life (QoL) data were also sought. A change in QoL may result from, for example, a reduction in hypoglycaemic episodes, and reduced fear of hypoglycaemia.

Participants

Adults, inclusive of any ethnic origin, over 18 years of age, who have been diagnosed with type 2 diabetes, defined using the WHO diagnostic criteria.[7]

Within those participant groups, we aimed to look at the effects in the following subgroups:

- Prior medications: metformin, sulphonylureas, insulin, DPP4 inhibitors (the gliptins)
- Patients with a duration of diabetes
  - Less than 2 years from diagnosis
  - 3–9 years' duration
  - Diagnosis for 10 years or longer

The hypothesis regarding duration is that since the mode of action is unrelated to insulin secretory function, the effect should not vary by duration of disease. Type 2 diabetes is often a progressive disease with diminishing β cell capacity.

Interventions

Any use of SGLT2 inhibitors (dapagliflozin and canagliflozin) in dual or triple therapy, in addition to other interventions including, but not restricted to: metformin, sulphonylureas, insulin and gliptins, compared to placebo or another active antidiabetic medication in combination with the same antidiabetic co-medication as in the SGLT2 inhibitor group. We have focused on doses likely to be used in clinical practice, namely 10 mg/day for dapagliflozin.

Outcome measures

The outcomes sought were

Primary outcome

- Glycaemic control as reflected in HbA1c.

Secondary outcomes

- Change in weight (kg) or body mass index (BMI).
- Change in QoL.
- Cardiovascular events.

Adverse effects, including hypoglycaemia and UTI.

Search methods for identification of studies

We searched the following sources:

- MEDLINE
- MEDLINE In-Process
- EMBASE
- The Cochrane Library, all sections
- NHS health technology assessment (HTA)
- Science Citation Index Expanded (SCI expanded)
- On-going Trials Registers
  - Clinical Trials (http://www.clinicaltrials.gov)
  - Current Control Trials (http://www.controlled-trials.com/)

- American Diabetes Association—Conference Abstracts
- European Association for the Study of Diabetes—Conference Abstracts
- Federal Drug Agency
- European Medicines Agency (EMEA)
- Scrutiny of bibliographies of retrieved papers

We searched for articles published since 2006, as this was the first recording of dapagliflozin on Ovid Technologies (OVID). An example of the SGLT2 dapagliflozin specific MEDLINE search strategy performed via the OVID interface is listed below:

1. dapagliflozin.mp.
2. BMS 512148.mp.
3. canagliflozin.mp.
4. JNJ 28431754.mp.
5. TA 7284.mp.
6. 1 or 2 or 3 or 4 or 5
7. SGLT2 inhibitor*.mp.
8. (sodium glucose adj6 inhibitor*).mp.
9. SGLT2 inhibitor*.mp.
10. (sodium-glucose adj6 inhibitor*).mp.
11. Sodium-Glucose Transporter 2/
12. sodium glucose-cotransporter 2.mp.
13. sodium-glucose co-transporter$.mp.
14. sodium glucose-cotransporter$.mp.

Reference lists of previous systematic reviews were checked for any trials not captured by the searches. The main search was carried out in October 2011. A search update in PubMed was carried out in July 2012.

Data collection and analysis

Study selection

Two reviewers selected studies independently using the defined inclusion and exclusions criteria above. Any resulting discrepancies were resolved by discussion, with minimal third-party mediation required.

Data extraction

A standardised data extraction form was used. Data extraction was by one reviewer, checked by a second. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary.

Quality assessment

The quality of the individual studies was assessed by one reviewer using the Cochrane Risk of Bias tool[6] and checked by a second reviewer. Quality was rated as 'high' if at least the first three criteria were fulfilled (adequate sequence generation, allocation concealment and blinding) and not more than one of the others was rated 'unclear'. Quality was rated as 'low' if these first three or any other four criteria were rated as unclear or inadequate. All the others were rated as 'medium' quality. Any disagreements were resolved by discussion.

Data synthesis and analysis

The data analysis has been reported according to the guide set down within the Cochrane Handbook for Systematic Reviews of Interventions.[6] Meta-analysis was carried out for comparing HbA1c and weight results for 10 mg dapagliflozin versus placebo in the intermediate term (12–26 weeks) and longer term (48–52 weeks) using a random effects model (inverse variance method) using the Cochrane Review Manager 5 software. Results were expressed as weighted mean differences (WMD) with 95% CI. Heterogeneity was assessed using the I^2 statistic. Where necessary, SDs were calculated from CIs or SEs as described in the Cochrane Handbook. In cases where means and measures of variation were only given in graphs but not in numerical form, values were estimated from graphs.

No meta-analysis using active comparators was performed due to clinical heterogeneity. Only two trials had active comparators, glipizide and sitagliptin, which have different modes of action and different effects on weight and hypoglycaemia risk.

RESULTS

Search results

The results of the literature search are shown in figure 1. After exclusions, made according to the study protocol, eight RCTs published in full, including 29 study arms, remained for analysis.

Study characteristics

The characteristics and results of the included studies are shown in table 1.

Study design

All included trials were double-blind RCTs, and all but one were placebo controlled. Trial durations ranged from 12 to 52 weeks (median 24 weeks). Most trials had longer-term extension periods (not completed/reported in all cases).

Study participants

Seven RCTs assessed dapagliflozin.[8–15] The dapagliflozin trials included 3398 participants. In the single canagliflozin trial,[16] 451 participants received that drug for 12 weeks.

Baseline HbA1c levels across the study populations ranged between 7.7% and 8.6% in most trials, but participants in one trial[9] had baseline HbA1c levels of 7.2%. Baseline BMI ranged between 31.2 and 36.2 kg/m^2, and mean age between 53 and 61 years.

Interventions

Dapagliflozin was administered orally, with doses ranging from 2.5 to 20 mg, used as once daily preparations. Doses of canagliflozin ranged from 50 to 300 mg administered once daily, with an additional group with 300 mg administered twice daily.

Background glucose-lowering drugs included metformin,[8 9 11 16] insulin,[15] glimepiride,[13] thiazolidinedione (TZD)[12] or combination therapy.[14 15]

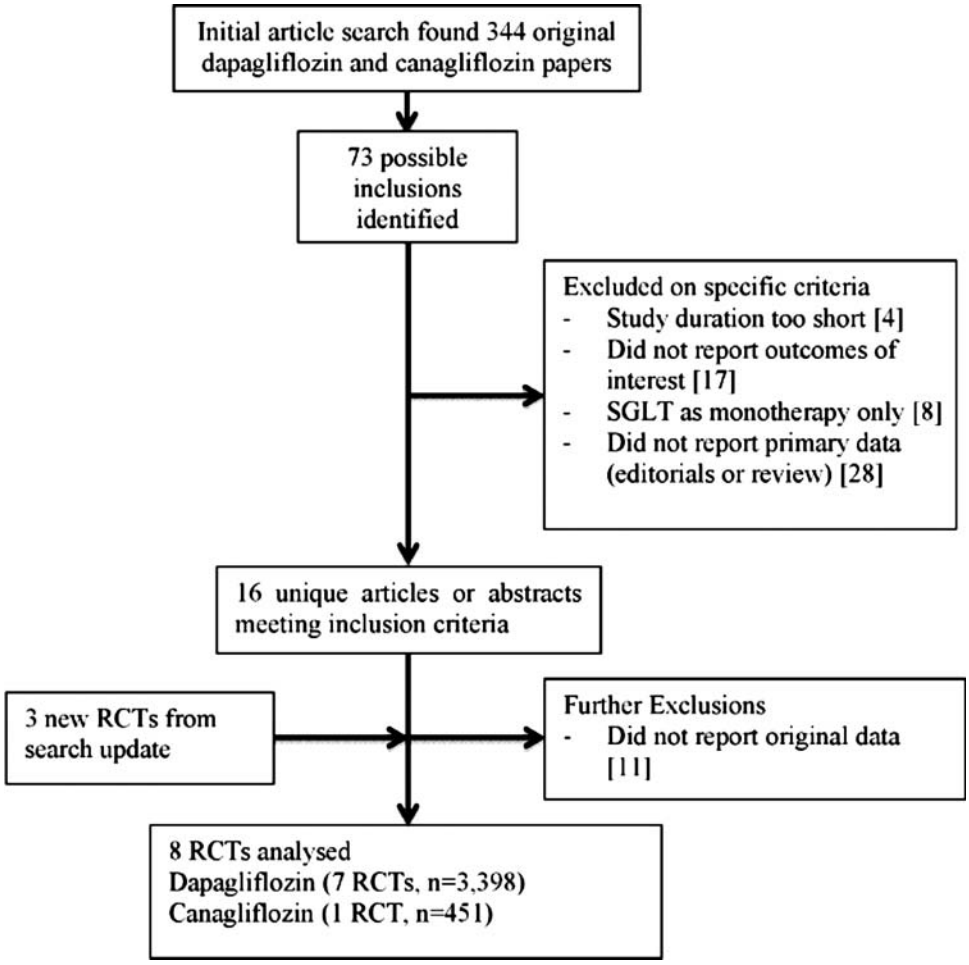

Figure 1 Search results.

Except for the study by Nauck,[11] all studies included a placebo group. Two studies included an active comparator: glipizide (mean dose 16 mg) in the study by Nauck,[11] and sitagliptin (100 mg) in the canagliflozin study.[16]

Most studies included lead in periods (median of 2 weeks) for assessing treatment adherence or stabilising background antidiabetic medication.

Outcome assessment

All studies reported on HbA1c, fasting plasma glucose (FPG), weight, blood pressure and safety parameters (including urinary or genital tract infections and hypoglycaemia). None of the studies reported QoL parameters.

Quality of included studies

Overall quality ratings are shown in table 1, details of risk of bias assessment are shown in table 2. The reporting quality was rated as 'high' in five of the studies,[8 9 11 13 15] 'medium' in two studies[14 16] and 'low' in one study.[12]

In five of the studies, both reporting of the generation of the randomisation sequence and of allocation concealment were adequate. All studies were at least double blind. Seven studies reported adequate intention-to-treat analysis (using the last observation carried forward method). Completion rates during the main study period were between 78% and 83%. Six of the studies included sample size calculations indicating that sufficient numbers of patients were recruited and included in order to detect a difference in HbA1c between 0.35% and 0.55% (median 0.5%). Seven studies explicitly reported that there were significant no differences in the main baseline characteristics between study groups. All studies were funded by the manufacturers.

Clinical effectiveness

Table 1 shows the difference between change from baseline to the main study end between 10 mg/day dapagliflozin and control groups (placebo or active control) for the main outcome measures. Detailed changes from baseline to the main study end or the end of any extension periods reported for all study groups are shown in online supplementary appendix.

Table 1 Study characteristics and outcomes (results reported for the end of the main study duration)

Study design	Participants	Interventions	Outcomes
Dapagliflozin			*Difference 10 mg dapagliflozin versus control (95% CI)*
Bailey *et al*[8]	N: 534	Intervention: 2.5, 5 or 10 mg dapagliflozin once daily	HbA1c (%): −0.54 (−0.74 to −0.34)
Design: multicentre (n=80), 4-arm, double-blind, placebo-controlled RCT	Age (years): 54–55 SD 9–10	Comparator: placebo	Weight (kg): −2.00 (−2.67 to −1.33)
Duration: 24 weeks	HbA1c (%): 7.9–8.2 SD 0.8–1.00	Background antidiabetic therapy:	FPG (mmol/l): −0.97 (95% CI NR)
Follow-up: 102 weeks	BMI (kg/m^2): 31.2–31.8 SD 5.4–6.2	metformin (≥1500 mg/day)	SBP (mm Hg): −4.9 (95% CI NR)
Quality: high			
Bolinder *et al*[9 10]	N: 180	Intervention: 10 mg dapagliflozin once daily	HbA1c (%):−0.29 (−0.42 to −0.16)
Design: multicentre (n=40), 2-arm, double-blind, placebo-controlled RCT	Age (years): 61 SD 7–8	Comparator: placebo	Weight (kg): −2.08 (−2.84 to −1.32)
Duration: 24 weeks	HbA1c (%): 7.2 SD 0.4–0.5	Background antidiabetic therapy: metformin (≥1500 mg/day)	FPG (mmol/L): −0.95 (−1.33 to −0.57)
Follow-up: 78 week extension	BMI (kg/m^2): 31.7–32.1 SD 3.9		SBP (mm Hg): −2.8 (−5.9 to 0.2)
Quality: high			
Nauck *et al*[11]	N: 801	Intervention: dapagliflozin once daily (mean dose 9.2 mg)	HbA1c (%): 0.0 (−0.11 to +0.11)
Design: multicentre (n=95), 2-arm, double-blind, active-controlled RCT	Age (years): 58–59 SD 9–10	Comparator: glipizide (mean dose 16.4 mg)	Weight (kg): −4.66 (−5.15 to −4.17)
Duration: 52 weeks	HbA1c (%): 7.7 SD 0.9	Background antidiabetic therapy:	FPG (mmol/l): −0.20 (95% CI NR)
Follow-up: 156 week extension	BMI (kg/m^2): 31.2–31.7 SD 5.1	metformin (≥1500 mg/day)	SBP (mm Hg): −5.1 (95% CI NR)
Quality: high			
Rosenstock *et al*[12]	N: 420	Intervention: 5 or 10 mg dapagliflozin once daily	HbA1c (%):−0.55 (−0.71 to −0.39)
Design: multicentre (n=105), 3-arm, double-blind, placebo-controlled RCT	Age (years): 53–54 SD 10–11	Comparator: placebo	Weight (kg): −1.78 (−2.32 to −1.24)
Duration: 24 weeks	HbA1c (%): 8.3–8.4 SD 1.0	Background antidiabetic therapy:	FPG (mmol/l): −1.33 (95% CI NR)
Follow-up: 24 week extension	BMI (kg/m^2): 51–62% ≥30; 87–93% ≥25	pioglitazone (30 or 45 mg/day)	SBP (mm Hg): −4.7 (95% CI NR)
Quality: low			
Strojek *et al*[13]	N: 592	Intervention: 2.5, 5 or 10 mg dapagliflozin once daily	HbA1c (%):−0.69 (−0.87 to −0.51)
Design: multicentre (n=84), 4-arm, double-blind, placebo-controlled RCT	Age (years): 59–60 SD 8–10	Comparator: placebo	Weight (kg): −1.54 (−1.88 to −1.20)
Duration: 24 weeks	HbA1c (%): 8.1 SD 0.7–0.8	Background antidiabetic therapy: glimepiride (4 mg)	FPG (mmol/l): −1.47 (−1.86 to −1.08)
Follow-up: 24 week extension	BMI (kg/m^2): 45–51% ≥30; 80–86% ≥25		SBP (mm Hg): −3.8 (−6.4 to −1.2)
Quality: high			
Wilding *et al*[14]	N: 71	Intervention: 10 or 20 mg dapagliflozin once daily	HbA1c (%):−0.70 (−1.07 to −0.33)

Continued

Table 1 Continued

Study design	Participants	Interventions	Outcomes
Design: multicentre (n=26), 3-arm, double-blind, placebo-controlled RCT	Age (years): 56–58 SD 7–11	Comparator: placebo	Weight (kg): −2.60 (−3.94 to −1.26)
Duration: 12 weeks	HbA1c (%): 8.4–8.5 SD 0.7–0.9	Background antidiabetic therapy: insulin (51–56 U)+OAD (≤79%	FPG (mmol/l): −0.86 (−2.13 to +0.42)
Follow-up: 4 weeks	BMI (kg/m^2): 34.8–36.2 SD 3.6–4.6	metformin only, ≤25% metformin	SBP (mm Hg): NR
Quality: medium		plus TZD, ≤12.5% TZD only)	
Wilding *et al*[15]	N: 800	Intervention: 2.5, 5 or 10 mg dapagliflozin once daily	HbA1c (%):−0.57 (−0.67 to −0.40)
Design: multicentre (n=126), 4-arm, double-blind, placebo-controlled RCT	Age (years): 59–60 SD 8–9	Comparator: placebo	Weight (kg): −2.04 (−2.57 to −1.51)
Duration: 24 weeks	HbA1c (%): 8.5–8.6 SD 0.8–0.9	Background antidiabetic therapy:	FPG (mmol/l): NR
Follow-up: 24+56 week extension	BMI (kg/m^2): 33.0–33.4 SD 5.0–5.9	insulin (77.1 U) ± OAD (~50%	SBP (mm Hg):
Quality: high		none, ~40% metformin only, rest combination)	−3.11 (−5.79 to −0.43)
Canagliflozin			*Difference versus active/placebo (95% CI)*
Rosenstock *et al*[16]	N: 451	Intervention: 50, 100, 200 or 300 mg once daily or 300 mg twice daily canagliflozin	HbA1c (%): −0.48–−0.73 vs placebo; +0.04–−0.21 vs sitagliptin (95% CI NR)
Design: multicentre (n=85), 7-arm, double-blind, placebo-controlled and active-controlled RCT	Age (years): 52.9 SD 8.1	Comparator 1: placebo	Weight (kg): −1.2–−2.3 vs placebo; −1.7–−2.8 vs sitagliptin (95% CI NR)
Duration: 12 weeks	HbA1c (%): 7.75 SD 0.93	Comparator 2: 100 mg once daily sitagliptin	FPG (mmol/l): −1.1–−1.7 vs placebo; −0.2–−0.8 vs sitagliptin (95% CI NR)
Follow-up: 2 weeks	BMI (kg/m^2): 31.5 SD 4.9	Background antidiabetic therapy:	SBP (mm Hg): +2.3–−3.6 vs
Quality: medium		metformin (≥1500 mg)	placebo; +1.8–−4.1 vs sitagliptin (95% CI NR) (roughly proportional to dose, but no advantage of 300 mg twice daily vs once daily)

BMI, body mass index; FPG, fasting plasma glucose; OAD, oral anti-diabetes drugs; RCT, randomised controlled trial; SBP, systolic blood pressure; TZD, thiazolidinedione.

Table 2 Study quality—risk-of-bias assessment

Study	Sequence generation	Allocation concealment	Blinding	Adequate handling of incomplete outcome data	Total drop out from drug assignment	No selective reporting	Groups comparable at baseline	Adequate power	Funder
Dapagliflozin									
Bailey *et al*[8]	Yes	Yes	Yes (double blind)	Yes—last observation carried forward	12%	Yes	Yes	Yes—0.5% HbA1c difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Bolinder *et al*[9]/ Ljunggren *et al*[10]	Yes	Yes	Yes (double blind)	Yes—last observation carried forward	7.1%	Yes	Yes	Unclear for primary endpoint, 2% BMD difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Nauck *et al*[11]	Yes	Yes	Yes (double blind and double dummy)	Yes—last observation carried forward	22.1%	Yes	Yes	Yes—0.35% HbA1c difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Rosenstock *et al*[12]	Not reported	Not reported	Yes (double blind)	Not reported	8% at 24 weeks, 19% at 48 weeks	Yes	Unclear	Not reported	Astra-Zeneca and Bristol-Myers-Squibb
Strojek *et al*[13]	Yes	Yes	Yes (double blind and double dummy)	Yes—last observation carried forward	8.5%	Yes	Yes	Yes—0.5% HbA1c difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Wilding *et al*[14]	Not reported	Not reported	Yes (single blind during lead in, double blind during study)	Yes—last observation carried forward	7%	Yes	Partially; matched for patient demographics, not for prior medications	Yes—0.5% HbA1c difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Wilding *et al*[15]	Yes	Yes	Yes (double blind and double dummy)	Yes—last observation carried forward	11% at 24 weeks, 15.5% at 48 weeks	Yes	Yes	Yes—0.5% HbA1c difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Canagliflozin									
Rosenstock *et al*[16]	Not reported	Not reported	Yes (double blind)	Yes—last observation carried forward	10.9%	Yes	Yes	Yes—0.55% HbA1c difference detectable	Janssen Global Services

BMD, bone mineral density.

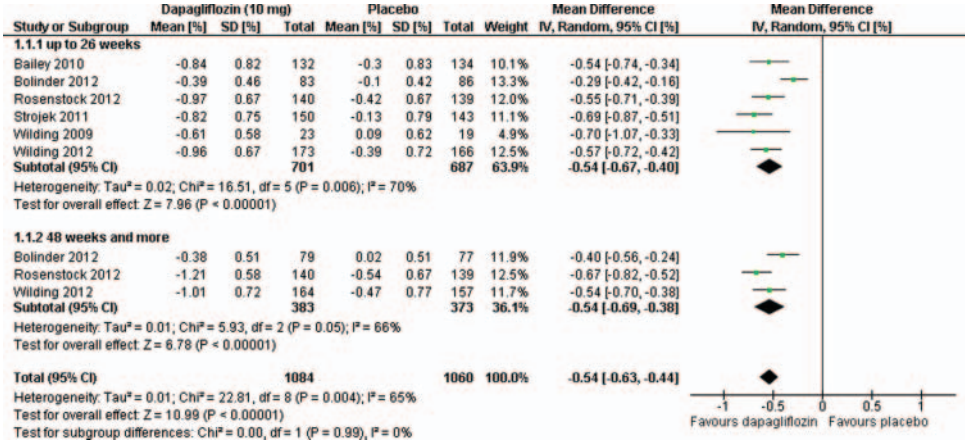

Figure 2 Meta-analysis for HbA1c change from baseline, 10 mg dapagliflozin versus placebo.

HbA1c levels

Figure 2 shows the results of the meta-analysis of 10 mg/day of dapagliflozin versus placebo for HbA1c for study durations up to 26 and for 48–52 weeks. Figure 3 shows the reductions in HbA1c in the seven study groups of the canagliflozin study[16] after 12 weeks of treatment.

Dapagliflozin at a dose of 10 mg/day significantly reduced HbA1c by (WMD) −0.54% (95% CI −0.67% to −0.40%, p<0.00001) after 12–26 weeks of treatment compared to placebo. There was significant heterogeneity, which was eliminated when excluding the only study with a baseline HbA1c<7.5%.[9] The WMD in HbA1c for studies with a baseline HbA1c value of >7.5% was −0.59% (95% CI −0.67% to −0.51%). Change from baseline in the 10 mg dapagliflozin groups ranged between −0.39% and −0.96% (main study end), and differences to placebo between −0.29% and −0.69%. HbA1c reductions at 48–52 weeks were similar to those at up to 26 weeks (three studies, WMD −0.54, 95% CI −0.69 to −0.38, p<0.00001).

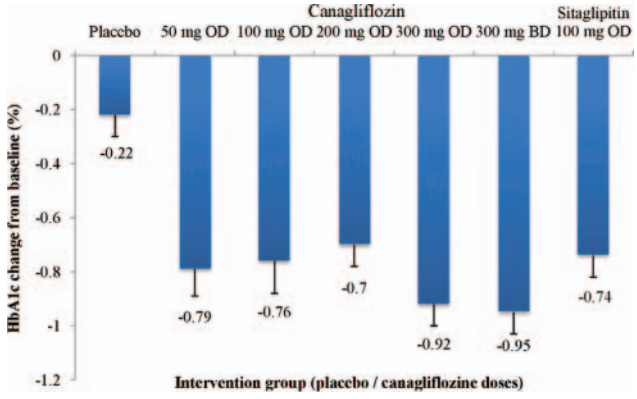

Figure 3 HbA1c change in response to canagliflozin (Rosenstock *et al*[16], means and SE).

In the study by Nauck,[11] there was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by −0.52% (95% CI −0.60% to −0.44%).

Canagliflozin reduced HbA1c in a dose-related manner up to 300 mg once daily (HbA1c reductions from baseline ranging from −0.70% to 0.95%) after 12 weeks of treatment, with only a small difference between once daily and twice daily doses at 300 mg (−0.92% SE 0.08 and −0.95% SE 0.08 from baseline, figure 3). The HbA1c reduction from baseline with sitagliptin was −0.74% SE 0.08.

Weight

Figure 4 shows the meta-analysis of weight change for 10 mg/day of dapagliflozin versus placebo for study durations up to 26 weeks and for 48–52 weeks. Dapaglifozin was associated with a significant reduction in weight. Compared to placebo, weight was reduced by −1.81 kg (WMD, 95% CI −2.04 to −1.57, p<0.00001, no significant heterogeneity) after up to 26 weeks of treatment. Weight reductions ranged from −0.14 to −4.5 kg in the 10 mg dapagliflozin groups and weight change ranged from +1.64 to −1.9 kg in the placebo groups. After 48–52 weeks of treatment, weight was reduced by −2.36 kg (WMD, 95% CI −2.85 to −1.88, p<0.00001, three RCTs) compared to placebo (range +0.69−−4.39 kg for the 10 mg dapagliflozin groups and +2.99 to −2.03 kg for the placebo groups). This reduction was significantly greater than the change at up to 26 weeks (p=0.04).

In the RCT comparing dapagliflozin to glipizide, weight decreased by −3.22 kg (95% CI −3.56 to −2.87) in the dapagliflozin arm after 52 weeks of treatment and increased by +1.44 kg (95% CI +1.09 to +1.78) in the glipizide arm (p<0.0001 between groups).[11] In the RCT of canagliflozin, weight was reduced by between −2.3 (SE 0.39) and −3.4 (SE 0.39) kg in the canagliflozin groups with similar reductions of −3.4 kg in the groups

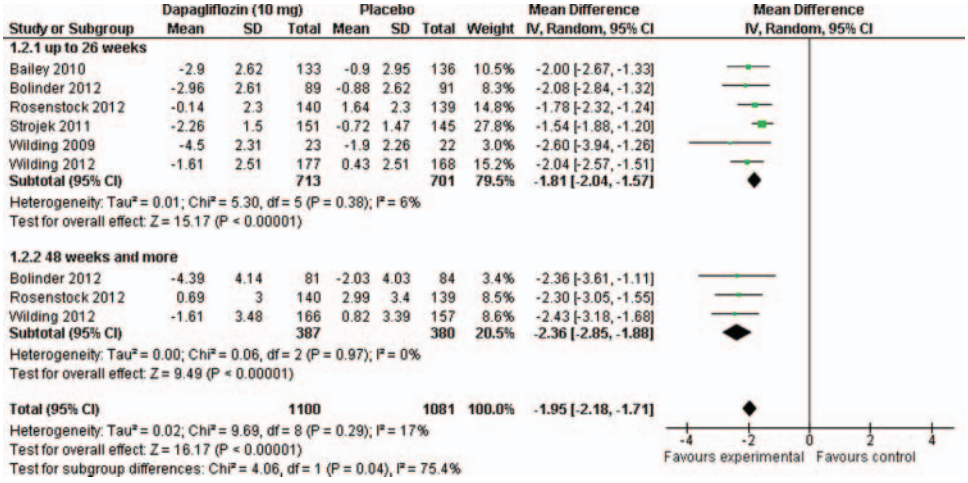

Figure 4 Meta-analysis for weight change from baseline, 10 mg dapagliflozin versus placebo.

receiving 300 mg once and twice daily (vs −1.1 SE 0.29 with placebo and −0.6 SE 0.39 with sitagliptin).[16]

Wilding *et al*[14] also recorded waist measurement, and reported reductions of 2.5 cm on dapagliflozin 10 mg daily and 1.3 cm on placebo.

Systolic blood pressure

Dapagliflozin produced a reduction in systolic blood pressure at all doses (p values generally not reported) ranging from −1.3 to −7.2 mm Hg in the 10 mg dapagliflozin groups compared to changes of +2 to −0.11 mm Hg in the control groups. Rosenstock *et al*[16] reported a systolic blood pressure reduction in response to canagliflozin ranging from −0.9 SE 1.7 mm Hg with 50 mg once daily to −4.9 SE 1.5 mm Hg with 300 mg once daily (−1.3 SE 1.5 mm Hg with placebo, −0.8 SE 1.4 mm Hg with sitagliptin).

Fasting plasma glucose

A significant reduction in FPG was seen in all dapagliflozin groups compared to placebo, with 10 mg dapagliflozin reducing FPG between −0.86 and −1.47 mmol/l more than control. There was no significant difference between FPG reductions with dapagliflozin versus glipizide in the study by Nauck.[11]

Canagliflozin reduced FPG by between −0.9 and −1.4 mmol/l (SE 0.20–0.22) with similar effects in the groups receiving 100, 200 or 300 mg once daily or 300 mg twice daily (vs +0.2 SE 0.20 mmol/l with placebo and −0.7 SE 0.20 mmol/l with sitagliptin).[16]

Adverse events

UTI and genital tract infection

Overall, there was a slight increase in the rate of UTIs when comparing 10 mg dapagliflozin with placebo (risk ratio 1.44, 95% CI 1.05 to 1.98, p=0.02), with a mean rate of 8.8% in the 10 mg dapagliflozin group (range 0–12.1%) and of 6.1% in the control groups (range 0–8.2%).

There was also an increase in genital tract infections when comparing 10 mg dapagliflozin with placebo (risk ratio 3.42, 95% CI 2.19 to 5.33, p<0.00001), with a mean rate of 9.5% in 10 mg dapagliflozin groups (range 0–12.3%) and 2.6% in the control groups (range 0–5.2%).

In most studies, the incidence on UTI or genital tract infections showed no dependence of dapagliflozin dose.

In the canagliflozin study, rates of UTIs ranged from 3.1% to 9.2% in the canagliflozin groups versus 6.1% with placebo and 1.5% with sitagliptin. Corresponding rates for genital tract infections were 3.1–7.8% in the canagliflozin groups, and 1.5% in both the placebo and the sitagliptin groups. There was no evidence of a dose dependence.[16]

In all cases the reported UTI and genital tract infections were not severe and resolved with simple treatment.

Hypoglycaemia

Overall, there was no significant difference in all types of hypoglycaemia between dapagliflozin and placebo groups. Hypoglycaemia, where data permitted, was divided into three categories: severe, moderate and other, corresponding, respectively, to capillary glucose readings of; <3.0 mmol/l (with external assistance required), <3.5 mmol/l, and symptoms suggestive of hypoglycaemia, but without confirming capillary glucose measurement. The incidence of all forms of hypoglycaemia in the dapagliflozin groups ranged from 1.1%[16] to 56.6% (ref. [15], any dose of dapagliflozin+insulin±oral anti-diabetes drugs (OAD)).

Wilding *et al*[14], reported more than a doubling of all hypoglycaemic events when dapagliflozin and insulin were compared to placebo and insulin (27% compared to 13%), but with only 16 hypoglycaemic episodes in a total of 71 participants.[14] Strojek *et al*[13] reported a small, dose independent, increase in hypoglycaemia from dapagliflozin 2.5, 5 and 10 mg, producing hypoglycaemia rates of 7.1%, 7.5% and 7.9%, respectively,

compared to 4.7% for placebo and glimepiride, however again with only a small number hypoglycaemic events, 29 among 592 participants. Nauck *et al*[11] reported that compared to glipizide, dapagliflozin produced a significant reduction in all types of hypoglycaemic events, with an incidence of 3.4% compared to 39.7% (14 vs 162 events).

Rosenstock *et al*[16], comparing placebo to canagliflozin, found a hypoglycaemic event rate of 2% in the placebo group, of 0–6% in the canagliflozin groups (highest rate in the 200 mg once daily group, no dose dependence), and 5% in the sitagliptin group. The severity was not commented on.

Other adverse events

Three studies reported deaths in dapagliflozin groups (Bolinder *et al* (2011) (one death), Strojek *et al* (2011) (two deaths), Wilding *et al* (2012) (two deaths)).[9] Causes of death were cardiopulmonary arrest, pulmonary embolism after ischaemic stroke, pneumonia due to oesophageal variceal haemorrhage, cardiogenic shock after aortic valve replacement and coronary bypass surgery, and acute myocardial infarction. None of the events considered to be the result of the study medication. Three deaths were reported by Nauck[11] in the glipizide group.

Six studies found similar rates of study discontinuation due to adverse events between the study groups, whereas two studies found slightly higher rates in the dapagliflozin groups (5.6% vs 0% in ref. [9], 9.1% vs 5.9% in ref. [11]). Five studies reported small numbers of renal impairment or failure in the different study groups and four of these reported no differences between study groups whereas in the study by Nauck *et al*[11], rates were slightly higher in the dapagliflozin than in the glipizide group (5.9% vs 3.4%). In one study, dapagliflozin was found to have no significant effect on bone formation and resorption or bone mineral density over 50 weeks of treatment.[9 10]

DISCUSSION

SGLT2 inhibitors, when used in combination therapies, and administered to individuals with type 2 diabetes who had previously reported poorly controlled blood glucose, were shown to be effective in

- Reducing HbA1c.
- Improving weight loss in conjunction with advice on lifestyle and diet.
- Lowering systolic blood pressure.
- Decreasing FPG levels.

Given the mechanism of action of the SGLT2 receptor inhibitors, the incidence and severity of hypoglycaemia would be expected to low.[17] Nauck *et al*[11] in one of the largest studies (801 participants), found a significantly higher incidence of hypoglycaemia in the sulphonylurea group, than with dapagliflozin. Hypoglycaemia in patients treated with SGLT2 receptor inhibitors was seen to be greatest when used in combination with insulin.

The present evidence suggests that the optimum dose of dapagliflozin may be 10 mg once daily, since there appears to be little additional benefit from increasing the dose to 20 mg. However, we have, at present, only one study evaluating the 20 mg dose, and then with only 23 patients allocated to that arm.

Implications for future practice

The number of glucose-lowering drugs for type 2 diabetes has been gradually increasing. We now have nine classes, though some contain only a single drug

- Metformin
- Sulphonylureas
- Pioglitazone
- Acarbose
- Meglitinide analogues, nateglinide and repaglinide
- GLP-1 analogues
- DPP-4 inhibitors
- SGLT inhibitors
- Insulins

The issue that arises is where the SGLT2 inhibitors fit into the therapeutic pathway. Factors to be considered include:

- Effect on glycaemic control as reflected in HbA1c reductions.
- Effect on weight, compared to other drugs, some of which cause marked weight gain.
- Adverse effects, particularly increased genital and urinary infections.
- Duration of effectiveness: some other drugs exhibit decreasing efficacy as duration of diabetes increases, especially those that act mainly by stimulating insulin release; the duration of action is unlikely to be affected by remaining levels of endogenous insulin production.
- Interactions with other drugs, especially in patients on treatment for comorbidities.
- Ease of use, by oral administration rather than injection.
- Cost.

The fear of hypoglycaemia can have a significant impact on the patient's QoL. The studies in this review recruited patients who were poorly controlled on present medications. Future trials might examine the role of the SGLT2 inhibitors in reducing the frequency of hypoglycaemic episodes in patients with good control but at the cost of hypoglycaemia. There is also the potential for their evaluation for use in poorly controlled type 1 diabetes.

Limitations of studies reviewed

There are no long-term data on SGLT2 side effects, both in terms of rare complications yet to be identified, but also on the long-term effects of significant glycosuria on the urinary tract. Two extension studies, published at present only as conference abstracts, reported that weight loss was maintained to 2 years. Del Prato *et al*,[18] in an extension of the Nauck study with 624 of the

original 801 participants, reported 2 year weight loss of 3.7 kg on dapagliflozin compared to a gain of 1.36 kg on glipizide. Wilding *et al*[19] in a follow-up of 64% of original participants, reported that by 2 years, weight had increased by 1.8 kg in the placebo group but had decreased by 1.4 kg in the 10 mg dapagliflozin group.

No studies in this review analysed their data by duration of diabetes. It is possible that the SGLT2 receptor inhibitors might be particularly useful in patients with longer duration in whom other agents such as the sulphonylureas may be becoming less effective due to loss β cell capacity.

Data of canagliflozin come from only one paper. Only two studies[14 15] examined the use of dapagliflozin in triple therapy, with insulin and no trials examined the role of the SGLT2 receptor inhibitors in triple oral therapy.

The costs of the drugs are not yet known, so cost-effectiveness cannot be assessed. The sulphonylureas are now very low cost, so the SGLT2 receptor inhibitors are very unlikely to be cost-effective compared to them. They are likely to be used in patients in whom metformin and sulphonylureas are insufficient or not tolerated, so the main comparators may be the gliptins, which have similar effects on HbA1c, are weight-neutral and which also increase the risk of UTIs, by about 40%.[20]

Musso *et al*[21] produced a systematic review of SGLT2 inhibitors that included 13 articles. The main reasons for the difference between our own review and that of Musso *et al* are our focus on a real-world use of SLGT2 inhibitors, and inclusion of recent trials. We excluded studies of less than 8 weeks in duration, while Musso *et al* analysed studies as short as 2 weeks. In addition, Musso *et al* included studies with SGLT2 inhibitors as primary intervention, while the present study has only looked at SGLT2 inhibitors as in combination therapy.

Musso *et al* reached similar conclusions to our own, namely that SLGT2 inhibitors are effective at reducing HbA1c and fasting plasma glucose levels and BMI, while also observing a reduction in serum uric acid and blood pressure. They concluded that there is an increased risk of UTIs with SGLT2 inhibitors, with an OR of 1.34, which is similar to our own findings.

The US Food and Drug Administration (FDA) reviewed dapagliflozin in July 2011.[22] They felt unable to approve it without additional safety data, mainly because of concerns about bladder and breast cancer. In the study data, there were nine cases of breast cancer in the dapagliflozin groups and none in the control groups. Some of these cancers occurred not long after dapagliflozin had been started. The absence of breast cancers among the controls was considered unexpected. An analysis by the manufacturers gave a standardised incidence ratio of 1.27 (95% CI 0.58 to 2.41) but this was not sufficient to reassure the FDA committee. There were nine cases of bladder cancer in those taking dapagliflozin and only one in the control groups, though it was noted that in five cases, haematuria had been recorded before dapagliflozin was started. The FDA committee noted that the imbalance might possibly be due to detection bias. The committee voted nine to six against approval.

CONCLUSIONS

The SGLT2 inhibitors are effective in lowering raised blood glucose, and as far as can be assessed from short-term results, appear safe. Their cost is not yet known, and so their place relative to other drugs is not yet clear. It is unlikely that dapagliflozin will be used as first-line monotherapy, on cost-effectiveness grounds.

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