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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]

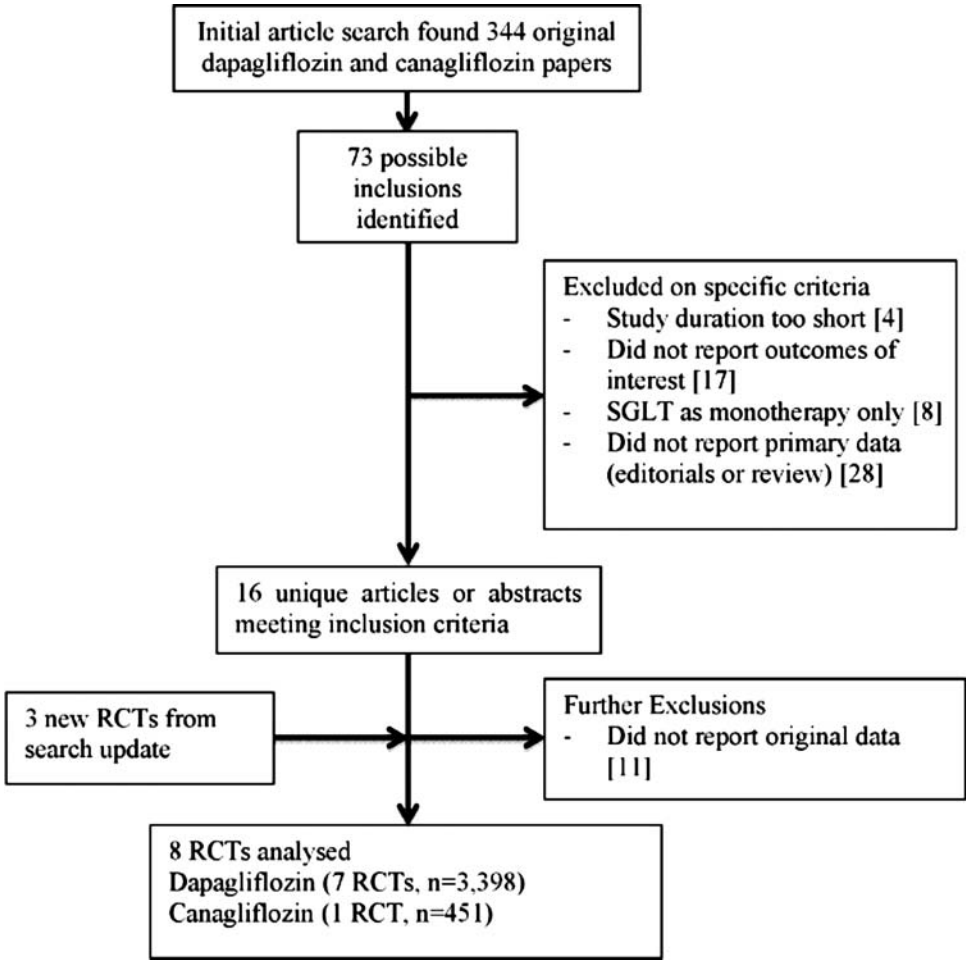

Figure 1 Search results.

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 Duration: 12 weeks Follow-up: 4 weeks Quality: medium Wilding *et al*[15]	Age (years): 56–58 SD 7–11 HbA1c (%): 8.4–8.5 SD 0.7–0.9 BMI (kg/m^2): 34.8–36.2 SD 3.6–4.6 N: 800	Comparator: placebo Background antidiabetic therapy: insulin (51–56 U)+OAD (≤79% metformin only, ≤25% metformin plus TZD, ≤12.5% TZD only) Intervention: 2.5, 5 or 10 mg dapagliflozin once daily	Weight (kg): −2.60 (−3.94 to −1.26) FPG (mmol/l): −0.86 (−2.13 to +0.42) SBP (mm Hg): NR HbA1c (%):−0.57 (−0.67 to −0.40)
Design: multicentre (n=126), 4-arm, double-blind, placebo-controlled RCT Duration: 24 weeks Follow-up: 24+56 week extension Quality: high Canagliflozin Rosenstock *et al*[16]	Age (years): 59–60 SD 8–9 HbA1c (%): 8.5–8.6 SD 0.8–0.9 BMI (kg/m^2): 33.0–33.4 SD 5.0–5.9 N: 451	Comparator: placebo Background antidiabetic therapy: insulin (77.1 U) ± OAD (~50% none, ~40% metformin only, rest combination) Intervention: 50, 100, 200 or 300 mg once daily or 300 mg twice daily canagliflozin	Weight (kg): −2.04 (−2.57 to −1.51) FPG (mmol/l): NR SBP (mm Hg): −3.11 (−5.79 to −0.43) *Difference versus active/placebo (95% CI)* 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 Duration: 12 weeks Follow-up: 2 weeks Quality: medium	Age (years): 52.9 SD 8.1 HbA1c (%): 7.75 SD 0.93 BMI (kg/m^2): 31.5 SD 4.9	Comparator 1: placebo Comparator 2: 100 mg once daily sitagliptin Background antidiabetic therapy: metformin (≥1500 mg)	Weight (kg): −1.2–−2.3 vs placebo; −1.7–−2.8 vs sitagliptin (95% CI NR) FPG (mmol/l): −1.1–−1.7 vs placebo; −0.2–−0.8 vs sitagliptin (95% CI NR) SBP (mm Hg): +2.3–−3.6 vs 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.

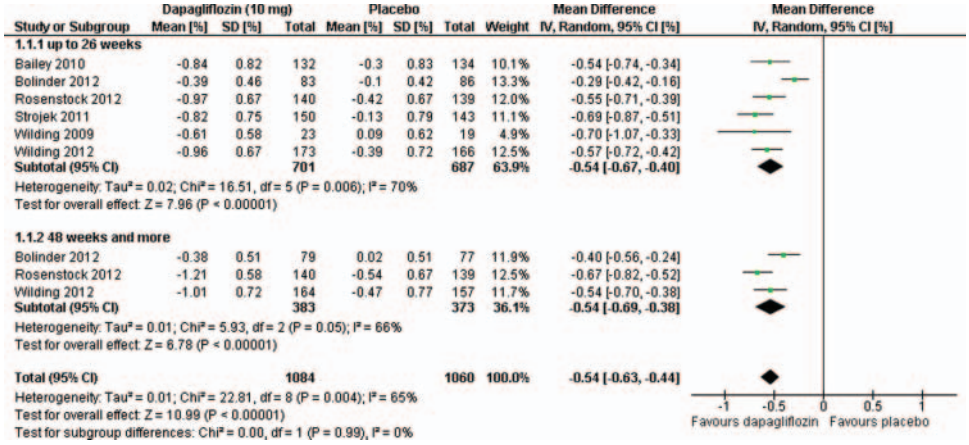

Figure 2 Meta-analysis for HbA1c change from baseline, 10 mg dapagliflozin versus placebo.

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).

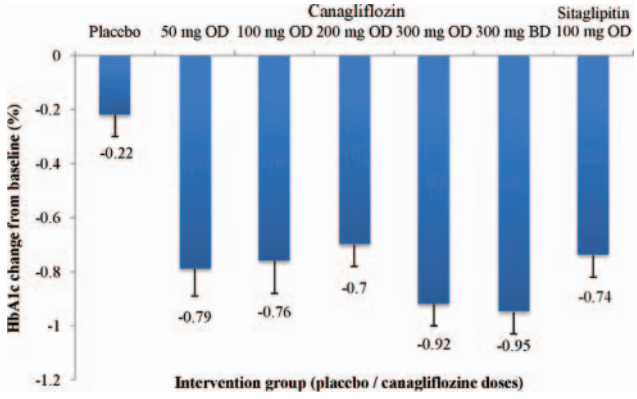

Figure 3 HbA1c change in response to canagliflozin (Rosenstock *et al*[16], means and SE).

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

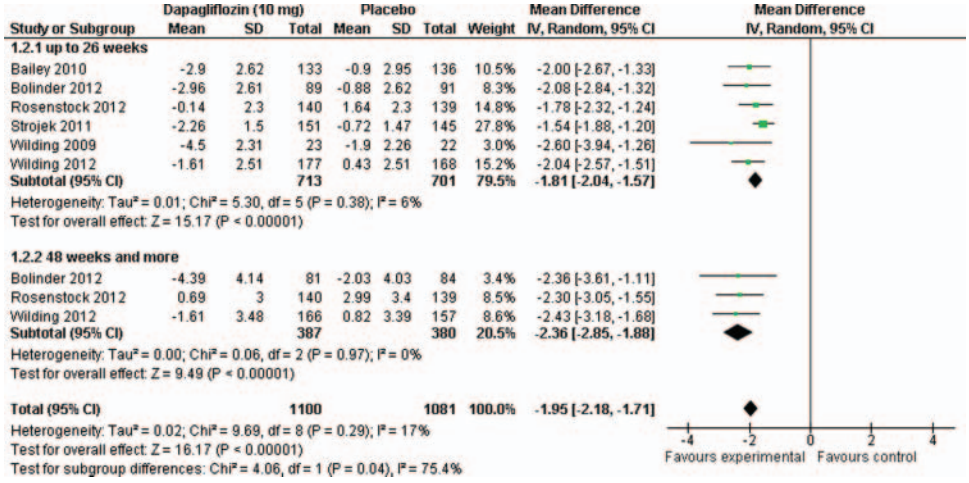

Figure 4 Meta-analysis for weight change from baseline, 10 mg dapagliflozin versus placebo.

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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Competing interests None

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Appendix – Detailed study data

Dapagliflozin

Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. **Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial.** Lancet 2010; 375: 2223-2233[8]				**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb
				SGLT2 inhibitor (2.5, 5 or 10 mg dapagliflozin) + metformin versus placebo + metformin
Aim: to determine the efficacy and safety of dapagliflozin in type 2 diabetes in patients with inadequate HbA1c control with metformin alone				
Study quality	High – see quality table for further information			
Study particulars	**Multi-centre:** 80 (USA, Canada, Argentina, Mexico, Brazil) **Duration of intervention**: 24 weeks **Duration of run in**: 2 weeks **Follow-up:** on completion of 24 weeks, a 102 week long-term study **Design:** 4-arm parallel-group RCT, double blind, placebo controlled **Primary outcome:** change from baseline in HbA1c at week 24 **Secondary outcomes:** At 24 weeks changes in: - Fasting plasma glucose - Proportion of patients achieving HbA1c <7%, number with HbA1c of 9% or more - Total bodyweight, change from baseline in bodyweight, and decreases in bodyweight of 5% or more - Laboratory tests, adverse events			
Participant criteria	**N:** 534 analysed **Inclusion criteria:** participants aged between 18 and 77 years; type 2 diabetes; BMI ≤45 kg/m^2; HbA1c 7 to 10.0%; fasting C-peptide ≥0.34 ng/ml; taking stable dose metformin ≥1500 mg per day **Exclusion criteria:** serum creatinine ≥133 µmol/L for men or ≥124 µmol/L for women (consistent with metformin labelling); urine albumin/creatinine ratio >203.4 mg/mmol; AST or ALT >three times the upper limit of normal; creatine kinase >three times the upper limit of normal, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with >10% weight loss during the 3 months before enrolment); systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg; any significant other systemic disease			
Interventions	**Intervention 1:** 2.5 mg dapagliflozin + metformin **Intervention 2:** 5 mg dapagliflozin + metformin **Intervention 3:** 10 mg dapagliflozin + metformin **Intervention 4:** matching placebo + metformin **OAD schedule:** metformin at pre-study dose (≥1500 mg/day; mean dose 1792 to 1861 mg/day); dapagliflozin once daily before morning meal **All groups:** diet and exercise counselling **Lead in period:** 2 weeks, single blind, to assess compliance with placebo, patients randomised after successful completion; metformin dose (open label 500 mg tablets) continued at pre-study levels			
Participant baseline data	**Group 1 (n analysed=134):** Placebo OD + metformin	**Group 2 (n=135):** 2.5 mg dapagliflozin OD + metformin	**Group 3 (n=133):** 5 mg dapagliflozin OD + metformin	**Group 4 (n=132):** 10 mg dapagliflozin OD + metformin
	Age: 53.7 SD10.3 years **Sex:** 55% male	**Age:** 55.0 SD9.3 years **Sex:** 51% male	**Age:** 54.3 SD9.4 years **Sex:** 50% male	**Age:** 52.7 SD9.9 years **Sex:** 57% male

	BMI (kg/m^2): 31.8 SD5.3 **HbA1c (%):** 8.11% SD0.96 **Duration of diabetes:** 5.8 SD5.1 years **FPG (mmol/L):** 9.19 SD2.57 **Systolic BP (mmHg):** 127.7 SD14.6		**BMI (kg/m^2):** 31.6 SD4.8 **HbA1c (%):** 7.99% SD0.90 **Duration of diabetes:** 6.0 SD6.2 years **FPG (mmol/L):** 8.96 SD2.39 **Systolic BP (mmHg):** 126.6 SD14.5		**BMI (kg/m^2):** 31.4 SD5.0 **HbA1c (%):** 8.17% SD0.96 **Duration of diabetes:** 6.4 SD5.8 years **FPG (mmol/L):** 9.39 SD2.72 **Systolic BP (mmHg):** 126.9 SD14.3		**BMI (kg/m^2):** 31.2 SD5.1 **HbA1c (%):** 7.92% SD0.82 **Duration of diabetes:** 6.1 SD5.4 years **FPG (mmol/L):** 8.66 SD2.15 **Systolic BP (mmHg):** 126.0 SD15.9	
Outcome (change from baseline to study end (week 24))								
	Group 1 (n=134): Placebo OD + metformin		**Group 2 (n=135):** 2.5 mg dapagliflozin OD + metformin		**Group 3 (n=133):** 5 mg dapagliflozin OD + metformin		**Group 4 (n=132):** 10 mg dapagliflozin OD + metformin	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
ΔHbA1c (%)	-0.3	-0.44 to -0.16	-0.67	-0.81 to -0.53 p=0.0002 vs placebo	-0.70	-0.85 to -0.56 p<0.0001 vs placebo	-0.84	-0.98 to -0.70 p<0.0001 vs placebo
ΔWeight (kg)	-0.9	-1.4 to -0.4	-2.2	-2.7 to -1.8 p<0.0001 vs placebo	-3.0	-3.5 to -2.6 p<0.0001 vs placebo	-2.90	-3.3 to -2.4 p<0.0001 vs placebo
ΔFPG (mmol/L)	-0.33	-0.62 to -0.04	-0.99	-1.28 to -0.69 p=0.0019 vs placebo	-1.19	-1.49 to -0.90 p<0.0001 vs placebo	-1.3	-1.60 to -1.00 p<0.0001 vs placebo
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
ΔSBP (mmHg)	-0.2	1.20	-2.10	1.10	-4.3	1.30	-5.10	1.30
HbA1c (%)	7.79	1.18	7.34	0.93	7.42	0.94	7.13	0.94
Adverse events **Safety assessment**: assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits								
	Minor hypoglycaemia = symptomatic episode, capillary glucose <3.5mmol/L **Major hypoglycaemia =** symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/L				**General events – where frequency is >5%** UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoT = Hypotension HypoG = Hypoglycaemia		**At least one or more adverse event** **Group 1 =** n=88 **Group 2 =** n=89 **Group 3 =** n=95 **Group 4 =** n=98	
	Group 1 (n analysed=134): Placebo OD + metformin		**Group 2 (n= 135):** 2.5 mg dapagliflozin OD + metformin		**Group 3 (n= 133):** 5 mg dapagliflozin OD + metformin		**Group 4 (n= 132):** 10 mg dapagliflozin OD + metformin	
Specific events	UTI n=11, GTI n=7 HypoT n=1, HypoG n=4 Events leading to discontinuation n=5		UTI n= 6, GTI n=11 HypoT n=0, HypoG n=3 Events leading to discontinuation n=3		UTI n=10, GTI n=18 HypoT n=2, HypoG n=5 Events leading to discontinuation n=3		UTI n=16, GTI n=12 HypoT n=0, HypoG n=5 Events leading to discontinuation n=4	
	Diarrhoea n=7 Back pain n=7 Nasopharyngitis n=11 Cough n=7 Influenza n=10 Hypertension n=6 Upper resp. tract Infection n=10 Headache n=6		Diarrhoea n=3 Back pain n=5 Nasopharyngitis n=12 Cough n=4 Influenza n=13 Hypertension n=9 Upper resp. tract Infection n=5 Headache n=4		Diarrhoea n=5 Back pain n=3 Nasopharyngitis n=4 Cough n=4 Influenza n=13 Hypertension n=4 Upper resp. tract Infection n=4 Headache n=1		Diarrhoea n=10 Back pain n=10 Nasopharyngitis n=8 Cough n=1 Influenza n=8 Hypertension n=5 Upper resp. tract Infection n=3 Headache n=11	

Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, Sugg J, Parikh S. **Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin.** Journal of Clinical Endocrinology and Metabolism 2012; 97(3): 1020-1031[9] Ljunggren Ö, Bolinder J, Johansson L, Langkilde AM, Sjöström CD, Sugg J, Parikh S. **Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin.** Diabetes, Obesity and Metabolism 2012 [E-publication ahead of print][10]	**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 inhibitor (10 mg dapagliflozin) + metformin versus placebo + metformin**
Aim: to confirm weight loss with dapagliflozin, and establish effect on body composition and bone metabolism in patients with type 2 diabetes with inadequate glucose control with metformin	
Study quality	High – see quality table for further information
Study particulars	**Multi-centre:** 40 (Bulgaria, Czech Republic, Hungary, Poland, Sweden) **Duration of intervention**: 24 weeks **Duration of run in**: 2 weeks **Follow-up:** 78 week extension period **Design:** 2-arm parallel group RCT, double blind, placebo controlled **Primary outcome:** change from baseline in total body weight at week 24 **Secondary outcomes:** At week 24: - Change in waist circumference and total fat mass - Proportion achieving weight reduction of >5% - HbA1c, fasting plasma glucose - Markers of bone formation and resorption - DXA assessment of bone mineral density and body composition - Systolic and diastolic blood pressure - Adverse events, laboratory values
Participant criteria	**N:** 180 analysed **Inclusion criteria:** participants with type 2 diabetes; postmenopausal women aged 55 to 75 years or men aged 30 to 75 years; HbA1C 6.5 to 8.5%; FPG ≤13.2 mmol/L; BMI ≥25 kg/m^2; weight ≤120 kg; treatment exclusively with a stable dose of metformin ≥1500 mg/day for at least 12 weeks before enrolment **Exclusion criteria:** men <30 years, perimenopausal women, HbA1c >8.5%, use of insulin within 6 months (except temporary ≤7 days); body weight change >5% within 3 months; calculated creatinine clearance <60 mL/min; urine albumin:creatinine ratio >1800 mg/g (>203.4 mg/mmol); ASP and/ALT and/or creatine kinase ≥3 times upper limit of normal range; serum total bilirubin >34 µmol/L; haemoglobin (Hb) ≤105 g/L (10.5 g/dL) for men and ≤95 g/L (9.5 g/dL) for women; abnormal thyroid stimulating hormone level; 25-hydroxyvitamin D level <12 ng/mL (<30 nmol/L); history of osteoporotic fracture, and other skeletal problems; metabolic bone disease or similar within 6 months of enrolment; SBP ≥180 mmHg and/or DBP ≥110 mmHg; congenital renal glycosuria; significant cardiac, renal, hepatic, respiratory, haematological, oncological, endocrine, immunological (including hypersensitivity to study medications), and alcohol and/or substance misuse disorders; pregnancy and/or lactation; a history of bariatric surgery; use of weight loss medication within 30 days of enrolment
Interventions	**Intervention 1:** 10 mg dapagliflozin + metformin **Intervention 2:** placebo + metformin **OAD schedule:** metformin at pre-study dose (≥1500 mg/day, mean dose 1901 mg SD430 in Group 1, 1989 mg SD477 in Group 2); dapagliflozin once daily before or with morning meal; in case of inadequate glycaemic control, sitagliptin 100 mg used as rescue medication **All groups:** diet, lifestyle, exercise counselling **Lead in period:** 2 weeks, single blind, placebo lead in

Participant baseline data	**Group 1 (start n= 91, analysed n=91):** Placebo + metformin		**Group 2 (start n= 91, analysed n= 89):** 10 mg dapagliflozin + metformin	
	Age: 60.8 SD6.9 years **Sex:** 56% male **BMI (kg/m^2):** 31.7 SD3.9 **HbA1c (%):** 7.16% SD0.53 **Duration of diabetes:** 5.5 SD5.3 years **FPG (mmol/L):** 8.3 SD1.4		**Age:** 60.6 SD8.2 years **Sex:** 55.1% male **BMI (kg/m^2):** 32.1 SD3.9 **HbA1c (%):** 7.19% SD0.44 **Duration of diabetes:** 6.0 SD4.5 years **FPG (mmol/L):** 8.2 SD1.4	
Outcome (change from baseline to study end (24 weeks))				
	Group 1 (n=91): Placebo + metformin		**Group 2 (n= 89):** 10 mg dapagliflozin + metformin	
	Mean	**95% CI**	**Mean**	**95% CI**
ΔHbA1c (%)	-0.10	-0.01 to -0.19 [from graph]	-0.39	-0.29 to -0.49 [from graph] , p<0.0001 vs placebo
ΔWeight (kg)	-0.88	-1.43 to -0.34	-2.96	-3.51 to -2.41, p<0.0001 vs placebo
ΔFPG (mmol/L)	+0.13	NR	-0.82	NR, p<0.0001 vs placebo
	Mean	**SD**	**Mean**	**SD**
ΔSBP (mmHg)	0.1	NR	-2.7	NR
Adverse events **Safety assessment:** assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits, laboratory tests and vital signs				
	Minor hypoglycaemia (HypoM) = symptomatic episode, capillary glucose <3.5mmol/L, asymptomatic episode with glucose <3.5 mmol/L **Severe hypoglycaemia** (HypoS) = symptomatic episode needing external assistance with capillary glucose <3.0mmol/L, recovery following glucose or glucagon administration **Other hypoglycaemia** (HypoO) = symptoms, but without confirmative measurement		**General events – where frequency is >2%** UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia other HypoT = Hypotension	**At least one or more adverse event** **Group 1 =** 42.9% **Group 2 =** 39.6% 1 death in dapagliflozin group, no deaths in placebo group No significant effect on bone formation and resorption or bone mineral density
	Group 1 (n=91): Placebo + metformin		**Group 2 (n= 89):** 10 mg dapagliflozin + metformin	
Specific events	UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO n=1 HypoT n=0 Events leading to discontinuation n=0		UTI n=6, GTI n=3 HypoM n=2, HypoS n=0, HypoO n=0 HypoT n=1 Events leading to discontinuation n=5	
	Nasopharyngitis n=5 Hypertension n=4 Pneumonia n=0 Angina pectoris n=0 Cystitis n=1 Arthralgia n=5 Headache n=2 Diarrhoea n=2		Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=3 Angina pectoris n=2 Cystitis n=2 Arthralgia n=1 Headache n=1 Diarrhoea n=0	

Nauck MA, Del Prato S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M, Parikh SJ. **Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycaemic control with metformin.** Diabetes Care 2011; 34: 2015-2022[11]		**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb
		SGLT2 inhibitor (up to 10 mg dapagliflozin) + metformin versus metformin + glipizide
Aim: to compare the efficacy, safety and tolerability of dapagliflozin with glipizide in patients with type 2 diabetes inadequately controlled with monotherapy		
Study Quality	High – see quality table for further information	
Study particulars	**Multi-centre:** 95 sites across 10 countries world-wide **Duration of intervention**: 52 weeks **Duration of run in**: 2 weeks **Follow-up:** on completion of 52 weeks, 156 week extension **Design:** 2-arm parallel group RCT, double-blind **Primary outcome:** absolute change from baseline in HbA1c at week 52 **Secondary outcomes:** - Change in total body weight - Proportion with hypoglycaemic episode - Proportion of ≥5% total weight loss	
Participant criteria	**N:** 801 analysed **Inclusion criteria:** participants aged 18 years and older; inadequately controlled type 2 diabetes (HbA1c >6.5 and ≤10%); BMI ≤45kg/m^2; fasting C-peptide ≥0.33 nmol/L, receiving stable dose metformin or metformin and one other OAD at up to half maximal dose for up to 8 weeks prior to enrolling; FPG ≤15 mmol/L **Exclusion criteria:** creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmol; AST and/or ALT and/or creatine kinase ≥3 times upper limit of normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSH; systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg; significant other disease	
Interventions	**Intervention 1:** dapagliflozin + metformin (dapagliflozin mean dose 9.2 mg/day) **Intervention 2:** glipizide + metformin (glipizide mean dose 16.4 mg/day) **OAD schedule:** metformin 1500 to 2000 mg/day (median dose at enrolment 2000 mg/day); dapagliflozin started at 2.5 mg, up-titrated to maximum tolerable dose (up to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up to 20 mg) **All groups:** diet and lifestyle advice **Lead in period:** before lead in: other OADs discontinued, metformin stabilised to 1500 to 2000 mg/day; 2 weeks single blind placebo lead in prior to randomisation	
Participant baseline data	**Group 1** (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin	**Group 2 (**start n= 408, analysed n= 401): 16.4 mg glipizide + metformin
	Age: 58 SD9 years **Sex:** 55.3% male **BMI (kg/m^2):** 31.7 SD5.1 **≥ 25 kg/m^2**: 95% **≥ 30 kg/m^2:** 57% **HbA1c (%):** 7.7% SD0.9 **Duration of diabetes:** 6 SD5 years **FPG (mmol/L):** 9.0 SD2.1	**Age:** 59 SD10 years **Sex:** 54.9% male **BMI (kg/m^2):** 31.2 SD5.1 **≥ 25 kg/m^2**: 90.8% **≥ 30 kg/m^2:** 55.4% **HbA1c (%):** 7.7% SD0.9 **Duration of diabetes:** 7 SD6 years **FPG (mmol/L):** 9.1 SD2.3

Outcome (change from baseline at study end (week 52))				
	Group 1 (n=400): 9.2 mg dapagliflozin + metformin		**Group 2 (n= 401):** 16.4 mg glipizide + metformin	
	Mean	**95% CI**	**Mean**	**95% CI**
ΔHbA1c (%)	-0.52	-0.60 to -0.44	-0.52	-0.60 to -0.44, NS
ΔWeight (kg)	-3.22	-3.56 to -2.87	+1.44	+1.09 to +1.78, p<0.0001
ΔFPG (mmol/L)	-1.24	-1.42 to -1.07	-1.04	-1.22 to -0.98, NS
ΔSBP (mmHg)	-4.3	-5.4 to -3.2 [from graph]	+0.8	-0.3 to 1.9 [from graph], p NR
Adverse events **Safety assessment:** assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits				
	Severe hypoglycaemia (HypoS) = symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/L **Minor hypoglycaemia** (HypoM) = symptomatic episode, capillary glucose <3.5mmol/L **Other hypoglycaemia** (HypoO) = symptoms, but without measurement confirming		**General events – where frequency is ≥3%** UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia other HypoT = Hypotension	**At least one or more adverse event** **Group 1 =** n=318 **Group 2 =** n=318 No deaths in dapagliflozin group 3 deaths in glipizide group
	Group 1 (n=406): 9.2 mg dapagliflozin + metformin		**Group 2 (n= 408):** 16.4 mg glipizide + metformin	
Specific events	UTI n=44, GTI n=50 HypoS n=0, HypoM n=7, HypoO n=7 HypoT n=6 Renal impairment / failure n=24 Events leading to discontinuation n=37 (0 due to hypoglycaemia)		UTI n=26, GTI n=11 HypoS n=3, HypoM n=147, HypoO n=40 HypoT n=3 Renal impairment / failure n=14 Events leading to discontinuation n=24 (6 due to hypoglycaemia)	
	Diarrhoea n=19 Nausea n=14 Vulvovaginal mycotic infection n=14 Back pain n=19 Nasopharyngitis n= 43 Cough n=15 Influenza n=30 Arthralgia n=11 Upper resp. tract Infection n=24 Headache n=21 Hypertension n=30		Diarrhoea n=26 Nausea n=15 Vulvovaginal mycotic infection n=2 Back pain n=20 Nasopharyngitis n=61 Cough n=20 Influenza n=30 Arthralgia n=21 Upper resp. tract Infection n=31 Headache n=17 Hypertension n=35	

Rosenstock J, Vico M, Wei L, Salsali A, List JF. **Effects of dapagliflozin, an SGLT2 inhibitor, on HbA1c, body weight, and hypoglycaemia risk in patients with type 2 diabetes inadequately controlled in pioglitazone monotherapy.** Diabetes Care 2012; 35: 1473-1478[12]			**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 inhibitor (5 or 10 mg dapagliflozin) + pioglitazone versus placebo + pioglitazone**
Aim: to examine the safety and efficacy of dapagliflozin added to pioglitazone in type 2 diabetes patients inadequately controlled on pioglitazone			
Study quality	Low – see quality table for further information		
Study particulars	**Multi-centre:** 105 (Argentina, Canada, India, Mexico, Peru, Philippines, Taiwan, USA) **Duration of intervention**: 24 weeks **Duration of run in**: 2 weeks **Follow-up:** 24 week extension period **Design:** 3-arm parallel group RCT, double blind, placebo controlled **Primary outcome:** change from baseline in HbA1c at week 24 **Secondary outcomes:** At week 24, change from baseline in: - Fasting plasma glucose - Postprandial glucose - Total body weight - Blood pressure - Adverse events, laboratory values, vital signs		
Participant criteria	**N:** 420 analysed **Inclusion criteria:** participants with type 2 diabetes; age ≥18 years; fasting C-peptide ≥1.0 ng/mL; BMI ≤45 kg/m^2; Group A: ≥12 weeks of pioglitazone 30 or 45 mg/day and HbA1c ≥7.0 to ≤10.5%; Group B: drug naïve for previous 10 weeks with HbA1c ≥8.0 to ≤11.0% or had received 15 mg/day pioglitazone or any dose of rosiglitazone with hbA1c ≥8.0 and ≤11.0% or had received ≥8 weeks of metformin ≤1700 mg/day or sulphonylurea ≤half maximal dose with HbA1c ≥7.0 to ≤11.0%, not more than one oral antidiabetic medication; Group B underwent 10 week dose optimisation in which initial therapy was discontinued and pioglitazone 30 mg/day was started and increased to 45 mg/day if possible; pre-randomisation HbA1c had to be ≥7.0 and ≤10.5% **Exclusion criteria:** AST or ALT >2.5 times upper limit of normal; total bilirubin >2.0 mg/dL, serum creatinine ≥2.0 mg/dL, urine albumin/creatinine ratio >1800 mg/g, calculated creatinine clearance <50 mL/min, congestive heart failure class III and IV		
Interventions	**Intervention 1:** 5 mg dapagliflozin + pioglitazone **Intervention 2:** 10 mg dapagliflozin + pioglitazone **Intervention 3:** placebo + pioglitazone **OAD schedule:** open-label pioglitazone 30 or 45 mg/day; dapagliflozin once daily; in case of inadequate glycaemic control (FPG >270 mg/dL (week 4 to 8) or >240 mg/dL (week 8 to 12) or >200 mg/dL (week 12 to 24) patients were eligible for open label rescue medication (metformin or sulphonylurea) **All groups:** diet and exercise counselling **Lead in period:** 2 weeks, single blind, placebo lead in		
Participant baseline data	**Group 1 (n=139):** Placebo + pioglitazone	**Group 2 (n=141):** 5 mg dapagliflozin + pioglitazone	**Group 2 (n=140):** 10 mg dapagliflozin + pioglitazone
	Age: 53.5 SD11.4 years **Sex:** 51.1% male **BMI:** 61.2% ≥30 kg/m^2; 87.8% ≥25 kg/m^2 **HbA1c:** 8.34% SD1.00	**Age:** 53.2 SD10.9 years **Sex:** 55.3% male **BMI:** 61.7% ≥30 kg/m^2; 86.5% ≥25 kg/m^2 **HbA1c:** 8.40% SD1.03	**Age:** 53.8 SD10.2 years **Sex:** 42.1% male **BMI:** 51.4% ≥30 kg/m^2; 92.9% ≥25 kg/m^2 **HbA1c:** 8.37% SD0.96

	Duration of diabetes: 5.07 SD5.05 years **FPG (mmol/L):** 8.92 SD2.61		**Duration of diabetes:** 5.64 SD5.36 years **FPG (mmol/L):** 9.36 SD2.89		**Duration of diabetes:** 5.75 SD6.44 years **FPG (mmol/L):** 9.15 SD2.57	
Outcome (change from baseline to study end)						
	Group 1 (n=139): Placebo + pioglitazone		**Group 2 (n=141):** 5 mg dapagliflozin + pioglitazone		**Group 2 (n=140):** 10 mg dapagliflozin + pioglitazone	
	Mean	**SE**	**Mean**		**Mean**	**SE**
ΔHbA1c (%)	*wk 24:* -0.42 *wk 48:* -0.54	0.08 0.08	-0.82 -0.95	0.08, p=0.0007 vs placebo 0.08, p NR	-0.97 -1.21	0.08, p<0.0001 vs placebo 0.07, p NR
ΔWeight (kg)	*wk 24:* +1.64 *wk 48:* +2.99	0.28 0.41	+0.09 +1.35	0.28, p<0.0001 vs placebo 0.38, p NR	-0.14 +0.69	0.28, p<0.0001 vs placebo 0.36, p NR
ΔFPG (mmol/L)	*wk 24:* -0.31 *wk 48:* -0.73	0.16 0.20	-1.38 -1.27	0.16, p<0.0001 vs placebo 0.18, p NR	-1.64 -1.84	0.16, p<0.0001 vs placebo 0.17, p NR
ΔSBP (mmHg)	*wk 24:* +1.3 *wk 48:* +2.0	1.2 1.2	-0.8 -1.0	1.2, p NS 1.1, p NR	-3.4 -2.2	1.2, p NS 0.7, p NR
Adverse events **Safety assessment:** assessed at every visit, questioning, laboratory tests and vital signs						
	Minor hypoglycaemia (HypoM) = symptomatic episode, capillary glucose <3.5mmol/L, asymptomatic episode with glucose <3.5 mmol/L **Severe hypoglycaemia** (HypoS) = symptomatic episode needing external assistance with capillary glucose <3.0mmol/L, recovery following glucose or glucagon administration **Other hypoglycaemia** (HypoO) = symptoms, but without confirmative measurement		**General events – where frequency is >5%** UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia other		**At least one or more adverse event** **Group 1 =** 66.9% **Group 2 =** 68.1% **Group 3** = 70.7%	
	Group 1 (n=139): Placebo + pioglitazone		**Group 2 (n=141):** 5 mg dapagliflozin + pioglitazone		**Group 2 (n=140):** 10 mg dapagliflozin + pioglitazone	
Specific events	UTI n=11, GTI n=4 Any hypoglycaemia n=1, HypoS n=0 Decreased renal function n=1 Events leading to discontinuation n=5		UTI n=12, GTI n=13 Any hypoglycaemia n=3, HypoS n=0 Decreased renal function n=2 Events leading to discontinuation n=5		UTI n=7, GTI n=12 Any hypoglycaemia n=0, HypoS n=0 Decreased renal function n=2 Events leading to discontinuation n=3	
	Dyslipidaemia n=9 Nasopharyngitis n=7 Diarrhoea n=6 Back pain n=4 Upper resp. tract infection n=10 Headache n=10 Pain in extremity n=1 Oedema peripheral n=9		Dyslipidaemia n=11 Nasopharyngitis n=7 Diarrhoea n=5 Back pain n=5 Upper resp. tract infection n=10 Headache n=3 Pain in extremity n=10 Oedema peripheral n=6		Dyslipidaemia n=16 Nasopharyngitis n=11 Diarrhoea n=9 Back pain n=8 Upper resp. tract infection n=7 Headache n=4 Pain in extremity n=4 Oedema peripheral n=3	

<table>
<tr><td colspan="4">Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of Dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes, Obesity and Metabolism 2011; 13(10): 928-938[13]</td><td>Funding source: Astra-Zeneca and Bristol-Myers-Squibb
SGLT2 Inhibitor (2.5, 5, or 10 mg dapagliflozin)plus glimepiride versus placebo plus glimepiride</td></tr>
<tr><td colspan="5">Aim: to determine the efficacy, safety and tolerability of dapagliflozin treatment, as an add-on therapy to glimepiride, in patients with inadequately controlled type 2 diabetes who had been treated with sulphonylurea monotherapy</td></tr>
<tr><td>Study quality</td><td colspan="4">High – see quality table for further information</td></tr>
<tr><td>Study particulars</td><td colspan="4">Multi-centre: 84 sites across 7 countries world-wide
Duration of intervention: 24 weeks
Duration of run in: 1 week for patients switched to glimepiride
Follow-up: on completion of 24 weeks, 24 week extension
Design: 4-arm parallel group RCT, double blind, placebo controlled
Primary outcome: change in HbA1c from baseline to week 24
Secondary outcomes:
After 24 weeks:
- Change in total body weight
- Change in post challenge plasma glucose (2 hrs) following oral glucose tolerance test
- Proportion of patients with HBA1c <7%
- Change in total body weight from baseline in patients with BMI ≥27kg/m^2
- Change in FPG</td></tr>
<tr><td>Participant criteria</td><td colspan="4">N: 592 analysed
Inclusion criteria: participants aged 18 years and older; inadequately controlled type 2 diabetes (HbA1c ≥7 to ≤10.0%); BMI ≤45kg/m^2; on stable sulphonylurea dose (at least half maximum dose (max 4 mg) for at least 8 weeks prior to enrolment); fasting C-peptide ≥0.33 nmol/ml; FPG ≤15 mmol/L
Exclusion criteria: creatinine clearance <50 mL/minor serum creatinine >177 µmol/L; urine albumin: creatinine ratio >203.4 mg/mmol; AST and/or ALT and/or creatine kinase ≥3 times upper limit of normal; total bilirubin >34 µmol/L; haemoglobin (Hb) ≤10 g/dL for men and ≤9.5 g/dL for women; SBP ≥180 mmHg and/or DBP ≥110 mmHg; any significant other systemic disease; pregnancy or lactation; use of weight loss medication within 30 days</td></tr>
<tr><td>Interventions</td><td colspan="4">Intervention 1: placebo + glimepiride
Intervention 2: 2.5 mg/day dapagliflozin + glimepiride
Intervention 3: 5 mg/day dapagliflozin + glimepiride
Intervention 4: 10 mg/day dapagliflozin + glimepiride
OAD schedule: open-label glimepiride 4 mg/day; glimepiride allowed to be down-titrated to 2 mg/day or discontinued in case of hypoglycaemia, no up-titration allowed; dapagliflozin once daily before the first meal of the day; in case of inadequate glycaemic control, patients could receive open-label rescue therapy of metformin, pioglitazone or rosiglitazone
All groups: all patients received dietary and lifestyle counselling; patients with BMI ≥27 kg/m^2 received advice about reducing caloric intake and increasing physical activity
Lead in period: 1 week for inclusion/exclusion review for those switched to 4 mg/day glimepiride</td></tr>
<tr><td rowspan="2">Participant baseline data</td><td>Group 1 (n= 146)
Placebo + glimepiride</td><td>Group 2 (n= 154)
2.5 mg dapagliflozin + glimepiride</td><td>Group 3 (n= 145)
5 mg dapagliflozin + glimepiride</td><td>Group 4 (n= 151)
10 mg dapagliflozin + glimepiride</td></tr>
<tr><td>Age: 60.3 SD10.16 years
Sex: 49% male</td><td>Age: 59.9 SD10.14 years
Sex: 50% male</td><td>Age: 60.2 SD 9.73 years
Sex: 50% male</td><td>Age: 58.9 SD 8.32 years
Sex: 43.7% male</td></tr>
</table>

	BMI: 86.2% ≥25 kg/m^2; 45.5% ≥30 kg/m^2 **HbA1c:** 8.15% SD0.74 **Duration of diabetes:** 7.4 SD5.7 years **FPG (mmol/L):** 9.58 SD2.07 **Systolic BP (mmHg):** 133.3		**BMI:** 84.4% ≥25 kg/m^2; 48.1% ≥30 kg/m^2 **HbA1c:** 8.11% SD0.75 **Duration of diabetes:** 7.7 SD6.0 years **FPG (mmol/L):** 9.56 SD2.13 **Systolic BP (mmHg):** 134.6		**BMI:** 80.3% ≥25 kg/m^2; 51.4% ≥30 kg/m^2 **HbA1c:** 8.12% SD0.78 **Duration of diabetes:** 7.4 SD5.7 years **FPG (mmol/L):** 9.68 SD2.12 **Systolic BP (mmHg):** 130.9		**BMI:** 79.5% ≥25 kg/m^2; 45% ≥30 kg/m^2 **HbA1c:** 8.07% SD0.79 **Duration of diabetes:** 7.2 SD5.5 years **FPG (mmol/L):** 9.55 SD2.04 **Systolic BP (mmHg):** 132.4	
Outcome (change from baseline to study end (week 24))								
	Group 1 (n= 146) Placebo + glimepiride		**Group 2 (n= 154)** 2.5 mg dapagliflozin + glimepiride		**Group 3 (n= 145)** 5 mg dapagliflozin + glimepiride		**Group 4 (n= 151)** 10mg dapagliflozin + glimepiride	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
ΔHbA1c (%)	-0.13	-0.26 to 0 [from graph]	-0.58	-0.7 to -0.46 [from graph], p<0.0001 vs placebo	-0.63	-0.76 to -0.5 [from graph], p<0.0001 vs placebo	-0.82	-0.94 to -0.7 [from graph], p<0.0001 vs placebo
ΔWeight (kg)	-0.72	-0.96 to -0.48 [from graph]	-1.18	-1.42 to -0.94 [from graph], NS	-1.56	-1.8 to -1.32 [from graph], p<0.0091 vs placebo	-2.26	-2.5 to -2.02 [from graph], p<0.0001 vs placebo
ΔFPG (mmol/L)	-0.11	-	-0.93	-	-1.18	-	-1.58	-
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
ΔSBP (mmHg)	-1.20	-	-4.7	-	-4.0	-	-5.0	-
Adverse events **Safety assessment:** assessed via adverse events from the Medical Dictionary or Regulatory Activties (MedDRA v12.1) via patient questionnaire and active questioning during visits; hypoglycaemic events, laboratory testing, vital signs								
	Hypoglycaemia not clearly defined				**General events – where frequency is ≥3% in any group** UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia		**At least one or more adverse event** **Group 1 =** n=69; **Group 2 =** n=80 **Group 3 =** n=70; **Group 4 =** n=76 1 death in dapagliflozin 2.5 mg 1 death in dapagliflozin 10 mg	
	Group 1 (n= 146) Placebo + glimepiride		**Group 2 (n= 154)** 2.5 mg dapagliflozin + glimepiride		**Group 3 (n= 145)** 5 mg dapagliflozin + glimepiride		**Group 4 (n= 151)** 10 mg dapagliflozin + glimepiride	
Specific events	UTI n=9, GTI n= 1 ≥ 1 Hypo n=7 Renal impairment / failure n=2 Events leading to discontinuation n=3		UTI n=6, GTI n=6 ≥ 1 Hypo n=11 Renal impairment / failure n=1 Events leading to discontinuation n=5		UTI n=10, GTI n=9 ≥ 1 Hypo n=10 Renal impairment / failure n=1 Events leading to discontinuation n=5		UTI n=8, GTI n=10 ≥ 1 Hypo n=12 Renal impairment / failure n=0 Events leading to discontinuation n=4	
	Bronchitis n=1 Diarrhoea n=5 Back pain n= 4 Nasopharyngitis n=4 Arthralgia n=4 Upper resp. tract Infection n=4 Hypertension n=6		Bronchitis n=2 Diarrhoea n=4 Back pain n=3 Nasopharyngitis n=3 Arthralgia n=6 Upper resp. tract Infection n=5 Hypertension n=8		Bronchitis n=3 Diarrhoea n=2 Back pain n=3 Nasopharyngitis n=8 Arthralgia n=0 Upper resp. tract Infection n=6 Hypertension n=2		Bronchitis n=5 Diarrhoea n=0 Back pain n=7 Nasopharyngitis n=5 Arthralgia n=1 Upper resp. tract Infection n=7 Hypertension n=2	

Wilding JPH, Norwood P, T'joen C, Bastien A, List JF, Fiedorek FT. **A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers. Applicability of a novel insulin-independent treatment.** Diabetes Care 2009; 32(9): 1656-1662[14]	**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 Inhibitor (10 or 20 mg dapagliflozin) + insulin + OAD versus placebo + insulin + OAD**
Aim: to determine if dapagliflozin lowers HbA1c in patients with type 2 diabetes poorly controlled with high insulin doses plus oral antidiabetic agents	
Study quality	Medium – see quality table for further information
Study particulars	**Multi-centre:** 26 (USA and Canada) **Duration of intervention**: 12 weeks **Duration of run in**: 2 weeks **Follow-up:** on completion of 12 weeks, 4 week follow-up **Design:** 3-arm parallel group RCT, double blind, placebo controlled **Primary outcome:** change from baseline in HbA1c at week 12 **Secondary outcomes:** - Change from baseline in FPG - Change in total daily requirement of insulin - Percentage of patients with change in HbA1c ≥0.5% - Percentage of patients with final HbA1c <7% - Change from baseline in total body weight - Change from baseline in post-prandial glucose - Adverse events, vital signs, laboratory measurements
Participant criteria	**N:** 71 analysed **Inclusion criteria:** participants aged between 18 and 75 years; type 2 diabetes; BMI ≤45 kg/m^2; HbA1c 7.5 to 10.0%; taking stable dose metformin (≥1000 mg) and/or pioglitazone (≥30 mg) or rosiglitazone (4 mg) for ≥6 weeks and insulin therapy ≥12 weeks before enrolment (≥50 units of U100, stable for ≥6 weeks); fasting C-peptide ≥0.8 ng/ml, serum creatinine <1.5 mg/dl (men) or <1.4 mg/dl (women), urine microalbumin-to-creatinine ratio <300 mg/g or, if exceeded on spot check, a 24-h urine total protein <3 g/24 h **Exclusion criteria:** type 1 diabetes, AST and/or ALT >2.5 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, symptoms of severely uncontrolled diabetes including a history of severe hypoglycaemia; any significant other disease
Interventions	**Intervention 1:** placebo + OAD + insulin **Intervention 2:** 10 mg dapagliflozin + OAD + insulin **Intervention 3:** 20 mg dapagliflozin + OAD + insulin **OAD/insulin schedule:** insulin dose reduced to 50% of pre-study daily insulin (total daily dose mean 51.3 to 55.7 U); dapagliflozin once daily; OAD: insulin sensitiser continued at pre-study dose (metformin ≥1000 mg and/or pioglitazone ≥30 mg or rosiglitazone 4 mg (66.7 to 79.2% metformin only, 8.3 to 25% metformin + TZD, 4.3 to 12.5% TZD only); no dose adjustments to OADs allowed; insulin could be down-titrated in patients at risk of hypoglycaemia **All groups:** diet and exercise programme (American Diabetes Association or similar local guidelines) **Lead in period:** 10-21 days to establish reduced insulin dose

Participant baseline data	**Group 1 (n=23):** Placebo + OAD + insulin		**Group 2 (n= 24):** 10 mg dapagliflozin + OAD + insulin		**Group 3 (n= 24):** 20 mg dapagliflozin + OAD + insulin	
	Age: 58.4 SD6.5 years **Sex:** 69.6% male **BMI (kg/m^2):** 34.8 SD4.6 **HbA1c:** 8.40% SD0.9 **Duration of diabetes:** 13.8 SD 7.3 years **FPG (mmol/L):** 9.22 SD 2.86 **Systolic BP (mmHg):** NR		**Age:** 55.7 SD9.2 years **Sex:** 54.2% male **BMI (kg/m^2):** 35.5 SD3.6 **HbA1c:** 8.4% SD0.7 **Duration of diabetes:** 11.8 SD5.8 years **FPG (mmol/L):** 8.67 SD 2.17 **Systolic BP (mmHg):** NR		**Age:** 56.1 SD10.6 years **Sex:** 54.2% male **BMI (kg/m^2):** 36.2 SD4.6 **HbA1c:** 8.5% SD0.9 **Duration of diabetes:** 11.3 SD5.6 years **FPG (mmol/L):** 8.98 SD 3.06 **Systolic BP (mmHg):** NR	
Outcome (change from baseline at study end (week 12))						
	Group 1 (n=23): Placebo + OAD + insulin		**Group 2 (n= 24):** 10 mg dapagliflozin + OAD + insulin		**Group 3 (n= 24):** 20 mg dapagliflozin + OAD + insulin	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
ΔHbA1c (%)	+0.09	-0.2 to +0.4	-0.61	-0.9 to -0.4	-0.69	-0.90 to -0.4, p NR
ΔWeight (kg)	-1.9	-2.9 to -0.9	-4.50	-5.5 to -3.5	-4.3	-5.3 to -3.3, p NR
ΔFPG (mmol/L)	+0.99	+0.08 to +1.90	+0.13	-0.75 to +1.02	-0.53	-1.42 to +0.35, p NR
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
ΔSBP (mmHg)	- (slight increase, NR)	-	-7.2	-	-6.10	-
HbA1c (%)	8.5	0.8	7.80	0.7	7.80	0.60
Adverse events **Safety assessment:** treatment-emergent adverse events, vital signs, laboratory measurements						
	Minor hypoglycaemia = symptomatic episode, capillary glucose <3.5mmol/L **Major hypoglycaemia =** symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/L		**General events – where frequency is >5%** UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoT = Hypotension, HypoG = Hypoglycaemia HypoS = major hypoglycaemia		**At least one or more adverse event** **Group 1 =** n=15 **Group 2 =** n=18 **Group 3 =** n=16	
	Group 1 (n=23): Placebo + OAD + insulin		**Group 2 (n= 24):** 10 mg dapagliflozin + OAD + insulin		**Group 3 (n= 24):** 20 mg dapagliflozin + OAD + insulin	
Specific events	UTI n=0, GTI n = 1 HypoT n=NR, HypoG n=3, HypoS n=1 Events leading to discontinuation n=1		UTI n= 0, GTI n = 0 HypoT n=NR, HypoG n=7, HypoS n=0 Events leading to discontinuation n=1		UTI n= 1, GTI n = 5 HypoT n=NR, HypoG n=6, HypoS n=0 Events leading to discontinuation n=1	
	Nausea n=1 Pollakiuria n=4 Back pain n=2 Nasopharyngitis n=2 Upper abdominal pain n= 2 Influenza n=2 Pain in extremity n=1 Upper resp. tract Infection n=2 Headache n= 2 Procedural pain n=2		Nausea n=1 Pollakiuria n=2 Back pain n=3 Nasopharyngitis n=2 Fatigue n=2 Influenza n=1 Pain in extremity n=2 Upper resp. tract Infection n=2 Headache n=3 Pharyngolaryngeal pain n=2		Nausea n=3 Pollakiuria n=3 Vomiting n=3 Vulvovaginal mycotic infection n=3 Anxiety n=2 Back pain n=2 Dry Mouth n=2 Nasopharyngitis n=2 Peripheral oedema n=2 Upper abdominal pain n=1 Fatigue n=1 Influenza n=1, Upper resp. tract Infection n=1 Pain in extremity n=1	

Wilding JPH, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, Parikh S. **Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin. A randomized trial.** Annals of Internal Medicine 2012; 156(6): 405-415[15]				**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb
				SGLT2 Inhibitor (2.5, 5 or 10 mg dapagliflozin) + insulin ± OAD versus placebo + insulin ± OAD
Aim: to evaluate the efficacy and safety of adding dapagliflozin to patients whose type 2 diabetes is inadequately controlled with insulin with or without oral antidiabetic drugs				
Study quality	High – see quality table for further information			
Study particulars	**Multi-centre:** 126 worldwide **Duration of intervention**: 24 weeks **Duration of run in**: 2 week enrolment **Follow-up:** on completion of 24 weeks, 24 week extension plus further 56 week extension in progress **Design:** 4-arm parallel group RCT, double blind, placebo controlled **Primary outcome:** change from baseline in HbA1c to week 24 **Secondary outcomes:** - Change in total body weight - Change in calculated mean daily insulin dose - Proportion with mean daily insulin reductions of ≥10% from baseline - Change in FPG - Laboratory tests, adverse events, vital signs			
Participant criteria	**N:** 800 analysed **Inclusion criteria:** participants aged between 18 and 80 years; type 2 diabetes; BMI ≤45 kg/m^2; inadequate glycaemic control (HbA1c ≥7.5 to ≤10.5%); stable insulin regimen with mean daily dose of ≥30 U for ≥8 weeks; additional treatment with up to two OADs allowed (≥1500 mg metformin or maximum tolerated dose or at least half maximum dose of other OADS for ≥8 weeks) **Exclusion criteria:** type 1 diabetes; signs of poorly controlled diabetes; calculated creatinine clearance <50 ml/min per 1.73 m^2 or serum creatinine ≥177 µmol/L, or if receiving metformin >133 µmol/L for men or ≥124 µmol/L for women			
Interventions	**Intervention 1:** placebo + insulin ± OAD **Intervention 2:** 2.5 mg dapagliflozin + insulin ± OAD **Intervention 3:** 5 mg dapagliflozin + insulin ± OAD **Intervention 4:** 10 mg dapagliflozin + insulin ± OAD **OAD/insulin schedule:** dapagliflozin once daily; open label treatment with usual daily dose of insulin (mean daily dose 77.1 U) and existing OADs (none in ~50%, metformin only in ~40%, metformin in combination in ~5 to 8%, other OAD / combination in ~1.5 to 6%); OAD doses could be decreased when hypoglycaemia was a concern; insulin could be up-or down-titrated if needed **All groups:** instructed to follow stable diet and exercise regimen; **Lead in period:** unclear			
Participant baseline data	**Group 1 (n analysed=193):** Placebo + insulin ± OAD	**Group 2 (n=202):** 2.5 mg dapagliflozin + insulin ± OAD	**Group 3 (n=211):** 5 mg dapagliflozin + insulin ± OAD	**Group 4 (n=194):** 10 mg dapagliflozin + insulin ± OAD
	Age: 58.8 SD8.6 years **Sex:** 49.2% male **BMI (kg/m^2):** 33.1 SD5.9 **HbA1c (%):** 8.47% SD0.77 **Duration of diabetes:** 13.5 SD7.3 years **FPG (mmol/L):** 9.5 SD3.2	**Age:** 59.8 SD7.6 years **Sex:** 49.5% male **BMI (kg/m^2):** 33.0 SD5.0 **HbA1c (%):** 8.46% SD0.78 **Duration of diabetes:** 13.6 SD6.6 years **FPG (mmol/L):** 10.0 SD3.3	**Age:** 59.3 SD7.9 years **Sex:** 47.4% male **BMI (kg/m^2):** 33.0 SD5.3 **HbA1c (%):** 8.62% SD0.89 **Duration of diabetes:** 13.1 SD7.8 years **FPG (mmol/L):** 10.3 SD3.3	**Age:** 59.3 SD8.8 years **Sex:** 44.8% male **BMI (kg/m^2):** 33.4 SD5.1 **HbA1c (%):** 8.57% SD0.82 **Duration of diabetes:** 14.2 SD7.3 years **FPG (mmol/L):** 9.6 SD3.0

	Systolic BP (mmHg): 136.1 SD17.2		**Systolic BP (mmHg):** 139.6 SD17.7		**Systolic BP (mmHg):** 137.8 SD16.2		**Systolic BP (mmHg):** 140.6 SD16.7	
Outcome (change from baseline to study end)								
	Group 1 (n analysed=193): Placebo + insulin ± OAD		**Group 2 (n=202):** 2.5 mg dapagliflozin + insulin ± OAD		**Group 3 (n=211):** 5 mg dapagliflozin + insulin ± OAD		**Group 4 (n=194):** 10 mg dapagliflozin + insulin ± OAD	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
ΔHbA1c (%)	*wk 24:* -0.39 *wk 48:* -0.47	-0.5 to -0.28 [graph] -0.59 to -0.35 [graph]	-0.79 -0.79	-0.89 to -0.69 [graph] -0.9 to -0.68 [graph] P<0.0001 vs placebo	-0.89 -0.96	-0.99 to -0.79 -1.07 to -0.85 p<0.0001 vs placebo	-0.96 -1.01	-1.06 to -0.86 -1.12 to -0.9 p<0.0001 vs placebo
ΔWeight (kg)	*wk 24:* 0.43 *wk 48:* 0.82	0.05 to 0.81 [graph] 0.29 to 1.35 [graph]	-0.92 -0.96	-1.29 to -0.55 -1.48 to -0.44 p<0.0001 vs placebo	-1.0 -1.0	-1.37 to -0.63 -1.52 to -0.48 p<0.0001 vs placebo	-1.61 -1.61	-1.98 to -1.24 -2.14 to -1.08 p<0.0001 vs placebo
ΔFPG (mmol/L)	*wk 24:* NR *wk 48:* NR	-	-0.65 -0.69	-1.19 to -0.11, p NR -1.28 to -0.11, p NR p<0.0001 vs placebo	-1.12 -0.90	-1.66 to -0.59, p NR -1.48 to -0.33, p NR p<0.0001 vs placebo	-1.10 -0.94	-1.64 to -0.56. p NR -1.53 to -0.36, p NR p<0.0001 vs placebo
ΔSBP (mmHg)	*wk 24:* -3.56 *wk 48:* -1.49	-5.47 to -1.64 -3.55 to 0.57	-4.21 -5.70	-6.05 to -2.38, p NR -7.25 to -3.34, p NR	-5.93 -4.33	-7.74 to -4.12, p NR -6.28 to -2.38, p NR	-6.66 -4.09	-8.53 to -4.80, p NR -6.09 to -2.09, p NR
Adverse events **Safety assessment**: adverse events, laboratory values, vital signs								
	Minor hypoglycaemia = symptomatic episode, capillary glucose <3.5mmol/L **Major hypoglycaemia =** symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/L **Other hypoglycaemia** = suggestive criteria not meeting criteria for major or minor hypoglycaemia				**General events – where frequency is ≥5%** UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoT = Hypotension HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia (other)		**At least one or more adverse event** **Group 1 =** n=144 **Group 2 =** n=153 **Group 3 =** n=153 **Group 4 =** n=145 2 deaths in the 5 mg dapagliflozin group	
	Group 1 (n analysed=193): Placebo + insulin ± OAD		**Group 2 (n=202):** 2.5 mg dapagliflozin + insulin ± OAD		**Group 3 (n=211):** 5 mg dapagliflozin + insulin ± OAD		**Group 4 (n=194):** 10 mg dapagliflozin + insulin ± OAD	
Specific events	UTI n=10, GTI n=5 HypoT n=2 HypoS n=2, HypoM n=99, HypoO n=11 Renal impairment / failure n=3 Events leading to discontinuation n=3		UTI n=16, GTI n=13 HypoT n=5 HypoS n=3, HypoM n=118, HypoO n=19 Renal impairment / failure n=2 Events leading to discontinuation n=2		UTI n=23, GTI n=21 HypoT n=5 HypoS n=2, HypoM n=113, HypoO n=24 Renal impairment / failure n=6 Events leading to discontinuation n=5		UTI n=20, GTI n=21 HypoT n=3 HypoS n=3, HypoM n=99, HypoO n=21 Renal impairment / failure n=4 Events leading to discontinuation n=5	
	Nasopharyngitis n=23 Headache n=15 Back pain n=11 Hypertension n=20 Diarrhoea n=8 Constipation n=3Peripheral oedema n=15 Upper resp. tract Infection n=12 Arthralgia n=11		Nasopharyngitis n=32 Headache n=11 Back pain n=11 Hypertension n=18 Diarrhoea n=7 Constipation n=12 Peripheral oedema n=8 Upper resp. tract Infection n=6 Arthralgia n=4		Nasopharyngitis n=35 Headache n=14 Back pain n=8 Hypertension n=16 Diarrhoea n=11 Constipation n=7 Peripheral oedema n=5 Upper resp. tract Infection n=8 Arthralgia n=3		Nasopharyngitis n=25 Headache n=5 Back pain n=11 Hypertension n=11 Diarrhoea n=10 Constipation n=6 Peripheral oedema n=9 Upper resp. tract Infection n=9 Arthralgia n=7	

Canagliflozin

Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Sha S, Arbit D, Usiskin K et al. **Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes.** Diabetes Care 2012; 35(6): 1232-1238[16]	**Funding source:** Janssen Global Services
	SGLT2 Inhibitor (50, 100, 200, or 300 mg OD or 300 mg BD canagliflozin) + metformin versus sitaglipitin + metformin versus placebo + metformin

Aim: to assess the safety, tolerability and efficacy of canagliflozin in patients with type 2 diabetes who have inadequate glycaemic control on metformin monotherapy

Study quality: Medium – see quality table for further information

Study particulars

Multi-centre: 85 (12 countries)
Duration of intervention: 12 weeks
Duration of run in: 4 weeks
Follow-up: 2 weeks post-treatment
Design: 7-arm parallel group RCT, double blind, placebo controlled
Primary outcome: change from baseline in HbA1c to week 12
Secondary outcomes:
- Change in FPG
- Change in weight
- Overnight glucose-to-creatinine ratio
- Change in proportion of participants with HbAc <7.0% and <6.5%
- Loss of beta cell function measured using HOMA2-%B
- Serum lipids
- Adverse events, laboratory assessments, vital signs

Participant criteria

N: 451 analysed
Inclusion criteria: participants with type 2 diabetes for ≥3 months; 18 to 65 years old; HbA1c level ≥7% and ≤10.5%; metformin monotherapy at a stable (≥3 months) dose of ≥1500 mg/day; stable body weight; BMI 25 (24 for Asians) to 45 kg/m^2; serum creatinine <1.5mg/dl for men and <1.4mg/dl for women
Exclusion criteria: not specifically reported

Interventions

Intervention 1: placebo (pla) + metformin
Intervention 2: canagliflozin (cana) 50 mg OD + metformin (met)
Intervention 3: canagliflozin 100 mg OD + metformin
Intervention 4: canagliflozin 200 mg OD + metformin
Intervention 5: canagliflozin 300 mg OD + metformin
Intervention 6: canagliflozin 300 mg BD + metformin
Intervention 7: sitagliptin (sita) 100 mg OD + metformin
OAD schedule: metformin mean dose 1890 SD479 mg/day
Lead in period: pre-treatment screening phase

Participant baseline data

	Group 1 pla + met (n=65)	**Group 2** cana 50 mg OD + met (n=64)	**Group 3** cana 100 mg OD + met (n=64)	**Group 4** cana 200 mg OD + met (n=65)	**Group 5** cana 300 mg OD + met (n=64)	**Group 6** cana 300 mg BD + met (n=64)	**Group 7** sita 100 mg OD + met (n=65)
Age (years)	53.3 SD7.8	53.3 SD8.5	51.7 SD8.0	52.9 SD9.6	52.3 SD6.9	55.2 SD7.1	51.7 SD8.1
Sex (% male)	48%	53%	56%	51%	56%	44%	58%

	BMI (kg/m^2)	30.6 SD4.6	31.7 SD4.6	31.7 SD5.0	31.4 SD5.2	31.6 SD4.9	31.8 SD5.2	31.6 SD5.0
	HbA1c (%)	7.75 SD0.83	8.00 SD0.99	7.83 SD0.96	7.61 SD0.80	7.69 SD1.02	7.73 SD0.89	7.64 SD0.95
	Diab. duration (years)	6.4 SD5.0	5.6 SD5.0	6.1 SD4.7	6.4 SD5.7	5.9 SD5.2	5.8 SD4.6	5.6 SD4.7
	FPG (mmol/L)	9.1 SD2.1	9.4 SD2.5	9.3 SD2.3	8.9 SD2.1	8.8 SD2.4	8.7 SD1.9	8.8 SD2.3
	SBP (mmHg)	125 SD10	127 SD11	127 SD13	124 SD11	126 SD12	128 SD13	129 SD13
Outcome (change from baseline at study end (12 weeks))								
	Group 1 pla + met (n=65)	**Group 2** cana 50 mg OD + met (n=64)	**Group 3** cana 100 mg OD + met (n=64)	**Group 4** cana 200 mg OD + met (n=65)	**Group 5** cana 300 mg OD + met (n=64)	**Group 6** cana 300 mg BD + met (n=64)	**Group 7** sita 100 mg OD + met (n=65)	
ΔHbA1c (%) [SE from graph]	-0.22 SE0.08	-0.79 SE0.1 p<0.001 vs placebo	-0.76 SE0.12 p<0.001 vs placebo	-0.70 SE0.08 p<0.001 vs placebo	-0.92 SE0.08 p<0.001 vs placebo	-0.95 SE0.08 p<0.001 vs placebo	-0.74 SE0.08 p<0.001 vs placebo	
ΔWeight (kg) [SE from graph]	-1.1 SE0.29	-2.3 SE0.39 p<0.001 vs placebo	-2.6 SE0.29 p<0.001 vs placebo	-2.7 SE0.39 p<0.001 vs placebo	-3.4 SE0.39 p<0.001 vs placebo	-3.4 SE0.29 p<0.001 vs placebo	-0.6 SE0.39 NS vs placebo	
ΔFPG (mmol/L) [SE from graph]	+0.2 SE0.20	-0.9 SE0.22 p<0.001 vs placebo	-1.4 SE0.22 p<0.001 vs placebo	-1.5 SE0.20 p<0.001 vs placebo	-1.4 SE0.22 p<0.001 vs placebo	-1.3 SE0.20 p<0.001 vs placebo	-0.7 SE0.20 p NR	
ΔSBP (mmHg)	-1.3 SE1.5	-0.9 SE1.7, p NR	+1.0 SE1.3, p NR	-2.1 SE1.8, p NR	-4.9 SE1.5, p NR	-3.6 SE1.4, p NR	-0.8 SE1.4, p NR	
Adverse events								
Safety assessment: adverse event reports (Medical Dictionary for Regulatory Activities), vital signs, physical examinations, laboratory assessments, self-administered vaginal swabs								
	Minor hypoglycaemia (HypoM) = symptomatic episode, capillary glucose <3.5mmol/l) **Severe hypoglycaemia** (HypoS) = symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/l) **Other hypoglycaemia** (HypoO) = symptoms, but without measurement confirming		**General events – where frequency is ≥10 participants** UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia HypoT = AEs suggestive of hypotension		**At least one or more adverse event** **Group 1 =** n=26 **Group 2 =** n=32 **Group 3 =** n=30 **Group 4 =** n=26 **Group 5 =** n=26 **Group 6 =** n=36 **Group 7 =** n=23			
		Group 1 pla (n=65)	**Group 2** cana 50 mg OD (n=64)	**Group 3** cana 100 mg OD (n=64)	**Group 4** cana 200 mg OD (n=65)	**Group 5** cana 300 mg OD (n=64)	**Group 6** cana 300 mg BD (n=64)	**Group 7** sita 100 mg OD (n=65)
Specific Events	UTI	n=4	n=3	n=2	n=6	n=2	n=3	n=1
	GTI	n=1	n=5	n=4	n=2	n=2	n=4	n=1
	Symptomatic Hypo	n=1	n=0	n=1	n=4	n=0	n=2	n=3
	HyopoT	n=1	n=0	n=4	n=3	n=1	n=1	n=1
	AEs leading to discontinuation	n=2	n=1	n=3	n=1	n=2	n=2	n=0
	Headache	n=2	n=1	n=5	n=2	n=3	n=1	n=1
	Nausea	n=0	n=3	n=1	n=1	n=3	n=5	n=1
	Nasopharyngitis	n=2	n=5	n=0	n=0	n=1	n=1	n=3
	Diarrhoea	n=2	n=1	n=1	n=0	n=2	n=3	n=2
	Pollakiuria	n=1	n=2	n=3	n=1	n=2	n=0	n=2
	Vulvovaginal mycotic infect.	n=0	n=4	n=2	n=4	n=1	n=3	n=1

Abbreviations: AE – adverse event; ALT – alanine transaminase; AST – aspartate transaminase; OD – once daily; BD – twice daily; BMD – bone mineral density; BMI – body mass index; BP – blood pressure; CI – confidence interval; DBP – diastolic blood pressure; FPG – fasting plasma glucose; NR – not reported; GTI – genital tract infection; NS – not significant; OAD – oral antidiabetic drug; SBP – systolic blood pressure; SD – standard deviation, SE – standard error; TZD – thiazolidinedione (pioglitazone or rosiglitazone); UTI – urinary tract infection; vs – versus; WMD – weighted mean difference