Title: 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 of the SGLT2 receptor inhibitors 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: 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: four trials published in full assessed dapagliflozin and one only available as a conference abstract assessed canagliflozin. Trial quality appeared good for the published trials. It could not be assessed for the trial available only as an abstract. Both drugs reduced HbA1c and also led to weight loss.

Limitations: trials were short term. No breakdown of relative effectiveness by duration was available. Data on canagliflozin is currently available from only one abstract. Costs of the drugs are not known so cost-effectiveness cannot be assessed.

Conclusions. Dapagliflozin appears effective and safe in type 2 diabetes.

Introduction

Type 2 diabetes is one of the most important and prevalent chronic diseases today, with in 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 (NICE), recommend that if lifestyle intervention is insufficient, the first line of drug

treatment is metformin, followed by a sulphonylurea, or sometimes a glitazone, before commencing on insulin. However sulphonylureas, glitazones and insulin all cause weight gain that 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 future anti-diabetic medications need to concentrate not only on a reduction in HbA1c, but ideally also on a reduction in cardiovascular disease.

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 (160-180mg/dl) has been reached. The proximal tubule cannot then reabsorb all of the filtered glucose, resulting in glucose passing into the urine. 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 to circulation, thereby reducing hyperglycaemia, without the side-effects of weight gain or hypoglycaemia (5). This systematic review will look at the clinical effectiveness of the new SGLT2 inhibitor drugs (dapagliflozin, also known under the synonym: BMS-512148, and canagliflozin (JNJ28431754)).

Review objectives

To assess the clinical effectiveness of the SGLT2 receptor inhibitors as part of dual and triple therapy

Decision Problem

This review assumed that the standard NICE guidelines had been previously followed with regard to the patient's management of type 2 diabetes i.e. Lifestyle changes and education initiated first, with the aim of reduction in weight via healthy diet and increased levels of physical activity.

We start from the position that the first-line drug in type diabetes will be metformin, and that the SGLT2 inhibitors will not be used in monotherapy.

The key questions for this review are therefore:

1. How does the clinical effectiveness of sodium glucose co-transporter 2 (SGLT2) inhibitors compare with that of current pharmacological interventions, when prescribed in dual therapy?

E.g. Metformin plus SGLT2 versus metformin plus sulphonylurea

2. How does the clinical effectiveness of the SGLT2 inhibitors compare with current options in triple therapy?

E.g. Metformin, sulphonylurea and SGLT2 inhibitor versus metformin, sulphonylurea and dipeptidyl peptidase 4 inhibitor (DPP4) such as sitagliptin

Under clinical effectiveness, we included glycaemic control, adverse effects and the effect of quality of life (QoL).

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

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 as:

- Plasma glucose (FPG)>11mmol/L after 2 hour oral glucose tolerance test,

Or

- Fasting glucose levels >7mmol/L. (6) with a second test to confirm in the absence of symptoms.

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

- Prior Medications: metformin, sulphonylureas, insulin, DPP 4 inhibitors (the gliptins)
- Patients with a duration of diabetes:
  - Less than 2 years from diagnosis
  - 3-9 years duration
  - Diagnosis longer than 10 years

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

Interventions:

- Any use of SGLT2 inhibitors in dual or triple therapy, in addition to other intervention including, but not restricted to: sulphonylureas, insulin, gliptins.

Outcomes measures.
The outcomes are:

- Glycaemic control as reflected in HbA1c – taken as the main outcome of interest
- Change in weight (Kg) or body mass index
- Adverse effects, including hypoglycaemia, urinary tract infections, change in quality of life (if data permitted)
- Cardiovascular events (if data permitted)

Study Design
Randomised control trials (RCT) and systematic reviews of trials are used for 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 measureable change to be detected in HbA1c levels due to turnover of red blood cells.

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

Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical effectiveness was undertaken systematically, following the general principles recommended in Cochrane Handbook for Systematic Reviews of Intervention (7)

Search methods for identification of studies

We searched the following sources:

- MEDLINE
- MEDLINE in-Process
- EMBASE
- The Cochrane Library, all sections
- NHS HTA
- Science Citation Index Expanded (SCI expanded)
- On-going Trials Registers:
- Clinical trials (www.clinicaltrials.gov)
- Current Control Trials (www.controlled-**trials**.com/)
- American Diabetes Association – Conference Abstracts
- EASD – 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. Initially returning 344 hits after the removal of duplications. 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. SGLT-2 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.

Data collection and analysis

Study Selection: two reviewers using the defined criteria above selected studies independently. Any resulting discrepancies were resolved by discussion, with minimal third party mediation required.

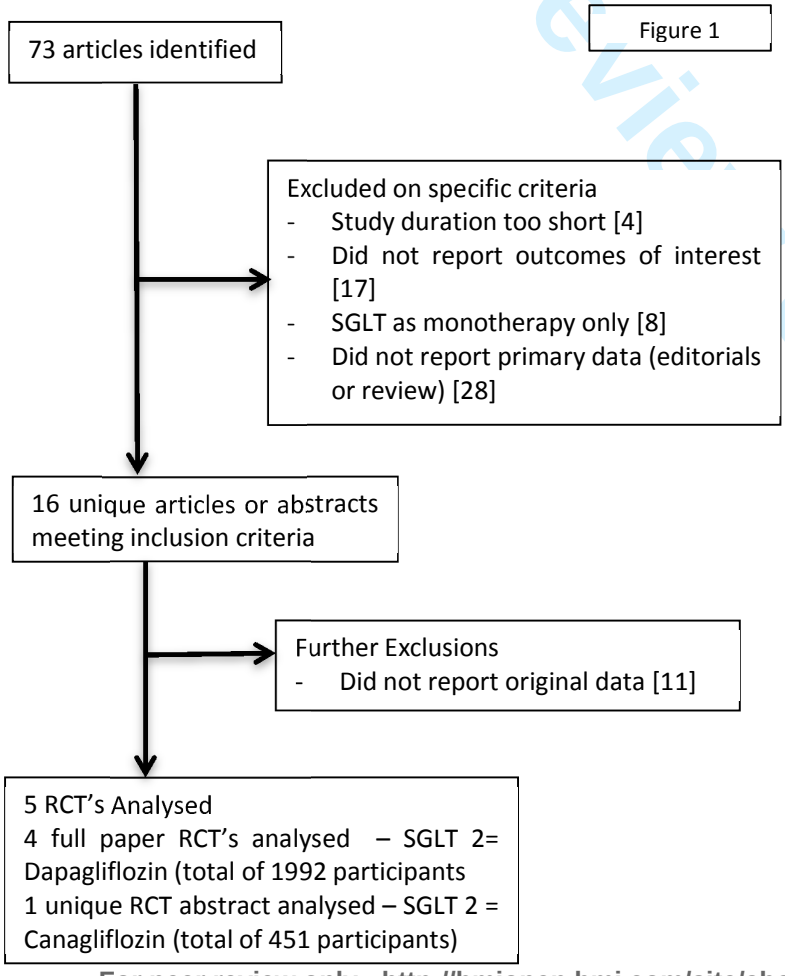
Data extraction: A standardised data extraction form was used. Data extraction was by one reviewer, checked by a second. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary.

The quality of the individual studies was assessed by one reviewer using the Cochrane Risk of Bias score (7) and independently verified by a second reviewer. Any disagreements were resolved by discussion.

Data synthesis and analysis

This data analysis has been reported according to the guide set down within the **Cochrane Handbook for Systematic Reviews of Interventions**, no meta-analysis was possible due to the small number and heterogeneity of trials.

Figure 1



The results of the literature search are shown in figure 1. After exclusions, made according to the study protocol, 4 RCTs published in full and 1 RCT available as an abstract covering 20 different comparisons remained for analysis.

Participants

Study participants

Four RCTs assessed dapagliflozin. 1,992 participants received dapagliflozin in total; across four RCTs, with trial durations ranging from 12 weeks to 54 weeks. In the single canagliflozin trial, 451 participants received that drug over a period of 12 weeks,

The median base-line HbA1c across the study populations was 8.14% (7.7-9.0%), median BMI of 32.7kg/m^2 (31.2 – 36.27kg/m^2) and median age of 56.2yrs (53 – 59.9yrs).

Interventions

Dapagliflozin was administered orally, with dose ranges from 2.5mg to 20mg, used as once daily preparations.

Canagliflozin dose ranged from 50mg to 300mg administered once daily, with additional 300mg group administered twice daily.

Background glucose-lowering drugs included insulin, glimepiride, thiazolidinedione (TZD), metformin and insulin, in combination or in isolation.

Lead in periods

In two studies, (Nauck and Bailey) the metformin dose was stabilised during a 2-week lead in period. Strojek (2011) stabilised glimepiride over an 8-week lead in.

Wilding (2009) stabilised all OADs over a 10-21 day run in, before fixing doses for the remainder of the study.

Only in the Rosenstock (2011) abstract canagliflozin, was no comment made as to pre-study stabilisation of Metformin.

Power

All studies included sample size calculations indicating that sufficient numbers of patients were recruited and included in order to detect a 0.5% difference in the outcomes of interest. The Nauck (2011) trial was able to detect 0.35% difference

Summary of Study Quality

Study	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
Bailey 2010	Yes	Yes (double-blind)	Yes – Last record carried forwards	12%	Yes	Yes	Yes – 0.5% difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Nauck 2011	Yes	Yes (Double	Yes – Last	22.1%	Yes	Yes	Yes - –	Astra-

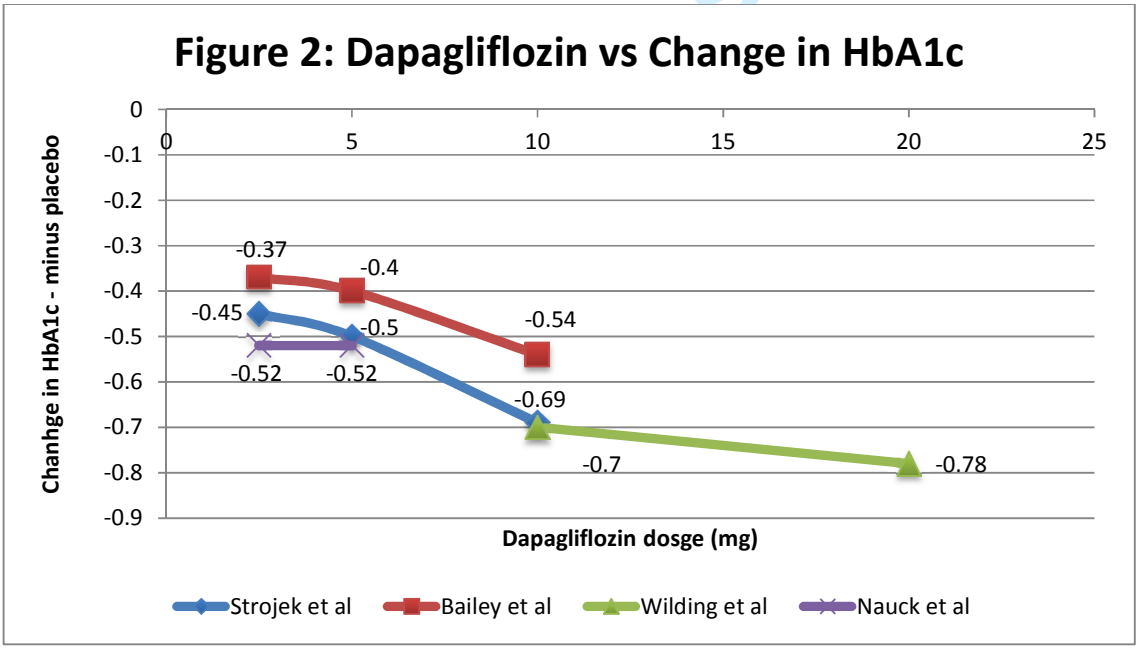
		Blinding and double dummy)	record carried forwards				0.35% difference detectable	Zeneca and Bristol-Myers-Squibb
Rosenstock 2010	Not reported	Yes (double blinding	Not reported	Not reported	Unclear	Yes	No comment on sample size calculation	*Johnson and Johnson*
Strojek 2011	Yes	Yes (Double Blinding and double dummy)	Yes – Last record carried forwards	8.5%	Yes	Yes	Yes – 0.5% difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Wilding 2009	Not reported	Single blind during lead in, double blind during study	Yes – Last record carried forwards	7.0%	Yes	Partially. Matched for patient demographics, not for prior medications	Yes – 0.5% difference detectable	Astra-Zeneca and Bristol-Myers-Squibb

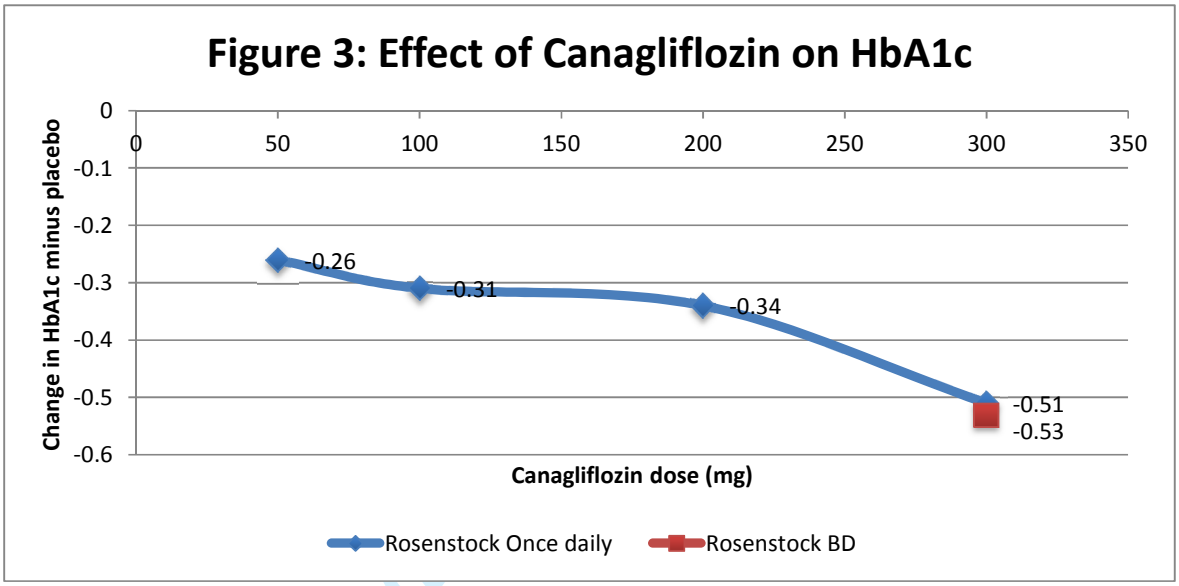
Results

HbA1c Levels

Figure 2 shows change in HbA1c (%) across different SGLT2 inhibitor doses, dapagliflozin from Strojek (2011), Nauck (2011), Bailey (2010) and Wilding (2009). Rosenstock (2010) shows the effect of canagliflozin on HbA1c (Figure 3)

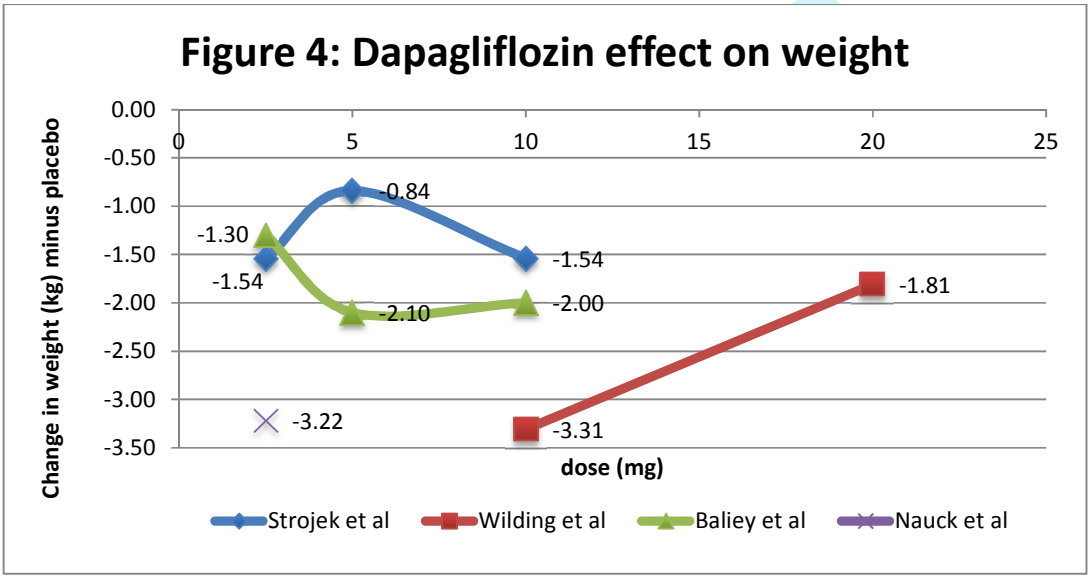
The SGLT2 inhibitors were shown, as demonstrated on Fig 2., to reduce HbA1c by between -0.52 and -0.78% when adjusted for changes on placebo. There was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by 0.52% (Nauck 2011).





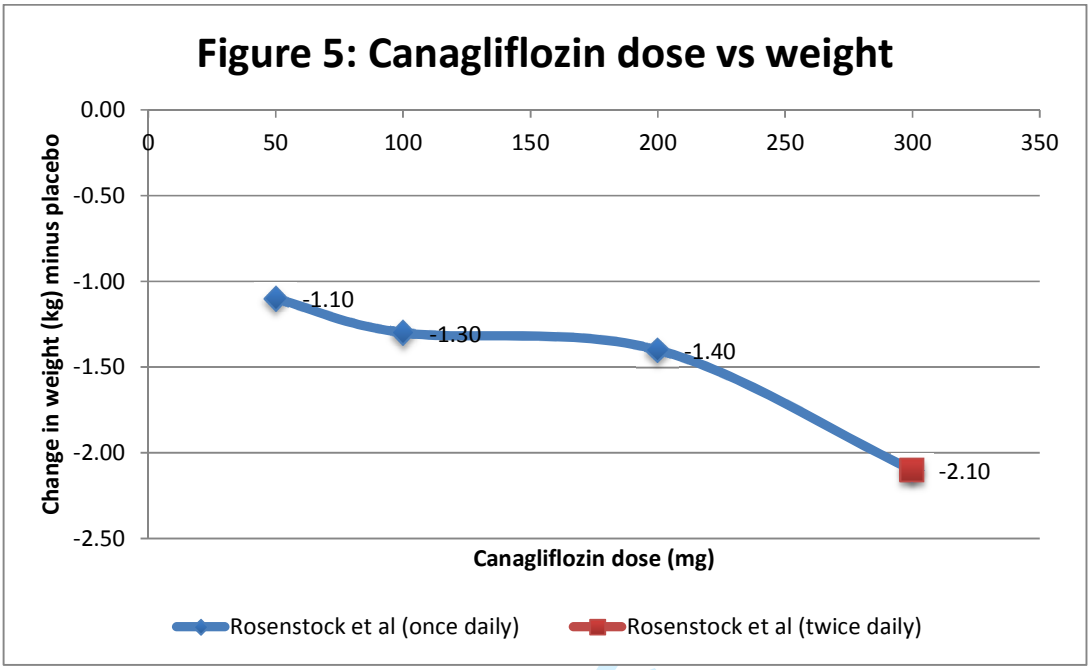
Body weight

Across all studies analysed, when comparing SLGT2 to both placebo and established OADs, SGLT2 inhibitors were associated with a significant difference in the change in total body weight, with a median weight reduction of -2.33kg (95% CI: -1.19 to -4.50) across all papers (figure 4), with the greatest reduction reported by Wilding (2009), (-4.50 kg, 10mg dapagliflozin, with reduction in insulin dosage accounted for), with the placebo group, glipizide and metformin reporting a +1.44kg weight gain. The lowest change from an SGLT2 was reported by Strojek, -0.84kg from 5mg dapagliflozin. Minor reductions in weight were reported for some comparators; OAD + insulin + placebo (-1.9kg); glimepiride + placebo (-0.72Kg, metformin alone (-0.9kg), however some of these effects were probably as a result of the trial effect, rather than a direct effect of the comparator drugs



The abstract for Rosenstock (2010) suggests that for both weight and HbA1c change, there was no difference in outcome between canagliflozin 300mg once daily and twice daily (fig 3)

Wilding (2009) also recorded waist circumferences during the study, finding on average a reduction of -1.7cm, -2.7 and -2.5cm in 2.5mg, 5mg and 10mg dapagliflozin groups, compared to -1.3cm in the placebo.



Systolic Blood Pressure

In placebo-controlled trials, dapagliflozin produced a significant reduction in systolic blood pressure at all doses, with an effect covering a range from -2.1 mmHg to -7.2 mmHg. The greatest reduction was reported by Wilding (2009), seen with dapagliflozin 10mg, but note that there were also changes in insulin dosage. Rosenstock (2010) did not report changes in systolic blood pressure with canagliflozin.

Fasting Plasma Glucose (FPG)

A significant change in FPG was seen in all dapagliflozin groups compared to placebo, with a range of -0.13 to -1.58 mmol/L (unadjusted for placebo) for SGLT2 inhibitors against +0.09 to -0.33mmol/L range for placebo, allowing a maximum reduction of -1.25 mmol/L to be attributed to 10mg dapagliflozin when given as an addition to glimepiride demonstrated by Strokjek (2011).

The reductions in FPG rose with SGLT2 dosage; as seen above with the 10mg dapagliflozin dose, Rosenstock (2010) further supported this by showing reductions in FPG from -0.9 to -1.8mmol/l across the 50 to 300mg canagliflozin dosage range, but with no increase in effect above 200mg once daily, indicating a ceiling of efficacy.

Adverse events

Urinary and genital tract infection

Nauck (2011) reported a significant increase in both UTI and GTI in the dapagliflozin (2.5mg) group – 44 UTIs and 50 GTIs, (10.8% and 12.3% respectively) compared to glipizide UTI 26, GTI 11) (6.3% and 2.6%). Amongst the other studies reviewed here, no other significant increase in UTI or GTI was seen. Bailey (2010) suggests that there is no dose related effect in terms of incidence of UTI and GTI for dapagliflozin, demonstrating no difference between dapagliflozin and placebo, with (11/7) (8.20/5.22%) UTI/GTI cases respectively for placebo vs 2.5mg, (6/11) (4.4/8.1%), 5mg ((5/18) (3.75/13.53%)) and 10mg (5/12) (3.78/9.0%). Wilding (2009) similarly reports few infections, with placebo ((0 and 1 (4.3%)), 5mg ((0 and 0) and finally 20mg (1/5) (4.3/21.7%)). When reported UTI and GTIs were not severe and resolved with simple treatment.

Hypoglycaemia

Compared to placebo, dapagliflozin intervention showed a small but not statistically significant, increase, in incidence of all forms of hypoglycaemia across three of the four dapagliflozin studies. Hypoglycaemia, where data permitted, was divided into three categories severe, moderate and other, corresponding respectively to capillary glucose readings of; <3.0Mmol/L, <3.5<Mmol/L, and "Symptoms suggestive of hypoglycaemia, but no confirming capillary glucose measurement taken". The incidence of all forms hypoglycaemia ranged from 2.2% (Bailey 2010 with 2.5mg dapagliflozin and metformin to 30.4%. (Wilding 2009, 10mg dapagliflozin + OAD + insulin.

Wilding (2009), reported more than a doubling of all hypoglycaemic events when dapagliflozin and insulin were compared to placebo and insulin, 15.7% compared to 30.4%, but with only 16 hypoglycaemic episodes in a total of 65 participants. Strojek reported a small increase in hypoglycaemia, but without evidence of a dose-response relationship with doses 2.5mg, 5mg and 10mg, producing hypoglycaemia rates of 7.1%, 7.5% and 7.9% respectively, compared to 4.7% for placebo and glimepiride, however again over only a small population of total hypoglycaemic events, 29 across the total 592 participants analysed.

Nauck (2011), indicates 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%, being 14 vs 150 events.

Other Adverse Events

Across all studies, two deaths were reported in dapagliflozin groups, both by Strojek (2011), attributed to cardiopulmonary arrest, and pulmonary embolism after ischaemic stroke respectively. Neither event was considered to be the result of the study medication.
Three deaths were also reported by Nauck (2011) in the glipizide placebo group, none in the SGLT2 group.

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:

i) Reducing HbA1c
ii) Improving weight loss in conjunction with advice on lifestyle and diet

iii) Lowering systolic blood pressure
iv) Decreasing FPG levels

Given the mechanism of action of the SGLT2 receptor inhibitors, hypoglycaemia would be expected to be less, and has been an important study outcome (8). Nauck (2011) 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 most when used in combination with insulin.

Strojek (2011) studied a range of doses (-0.58, -0.63 and -0.82% HbA1c reduction, with 2.5mg, 5mg, and 10mg respectively) from which it appear that the optimum dosage of dapagliflozin would appear to lie within the 10-20mg ranges, in terms of reducing HbA1c outcome.

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
- The sulphonylureas
- Pioglitazone
- Acarbose
- The meglitinide analogues, nateglinide and repaglinide
- The GLP-1 analogues
- The DPP-4 inhibitors
- The 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 weight gain
- Adverse effects, particularly increased genital and urinary infections
- Duration of effectiveness. Some other drugs lose efficacy as duration of diabetes increase, especially those that act mainly of partly 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 co-morbidities
- Ease of use, by oral administration rather than injection
- Cost

The fear of hypoglycaemia can have a significant impact on the patient's quality of life. 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 I diabetes.

Limitations of studies reviewed

There are no long-term data on SGLT2 side effects, both in terms of rare complications yet to be established, but also on the long-term effects of significant glycosuria on the urinary tract. Wilding (2009) noted one occurrence of renal failure reported in the dapagliflozin group

No studies in this review analysed the 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 beta cell capacity.

Wilding et al matched for demographics between participants, but not for prior medications – it is therefore possible that this may have contributed to a statistically significant imbalance on these parameters

Musso et al (2010) (9) produced an early systematic review into SGLT2 inhibitors evaluated on an intention to treat principle, covering a breadth of 151 articles. The main reason for the difference in number of studies between our own review and Musso et al, is our focus is towards a very real world use of SLGT2 inhibitors. We excluded studies of less than 8 weeks in duration, whilst Musso et al analysed studies as short as 2 weeks. In addition, Musso et al included studies with SGLT2 inhibitors are primary intervention, whilst this study has only looked at SGLT2 inhibitors as in combination therapy.

Musso et al reach similar conclusions to our own, namely that SLGT2 inhibitors are effective at reducing HbA1c and fasting plasma glucose levels and BMI, whilst also observing a reduction in serum uric acid and blood pressure.

They come to similar conclusions about a ceiling of effectiveness for dapagliflozin doses of approximately 10-20mg/d

Musso et al conclude there is an increased risk of UTI with SGLT2 inhibitor, with an odds ratio of 1.34. The present review was unable to conclusively determine the effect of SGLT2 inhibitors on UTI/GTI, however it is likely, from the strength of the Nauck paper, that there is an associated increase, but of only mild infections not requiring treatment.

Conclusion

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.

Competing interests of authors

None

Funding source – internal department

References

1. Diabetes UK,
Diabetes in the UK 2010: Key statistics on Diabetes
http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf
(Accessed October 1st 2011)

2. Mokdad AH, Ford ES, Bowman BA, Dietz W, Vinicor F, Bales V, Marks J.
Prevalence of Obesity, Diabetes, and Obesity-Related Health Risk Factors, 2001
A. JAMA. 2003;289(1):76-79. doi: 10.1001/jama.289.1

3. Stone PH, Muller JE, Hartwell T.
The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis.
J. *Am Coll Cardiol.* 1989;14:49–57

4. Santer R., Kinner M., Lassen CL., Schenppenheim R, Eggert P, Bald M, et al
Molecular Analysis of the SGLT2 Gene in Patients with Renal Glucosuria.
JASN November 1, 2003vol. 14 no. 11 2873-2882

5. Hanefeld M.
Dapagliflozin, an SGLT2 inhibitor, for diabetes.
Lancet Volume 375, Issue 9733, 26 June 2010-2 July 2010, Pages 2196-2198

6. **Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications.**
Report of a WHO Consultation, WHO/NCD/NCS/99.2 (2000)
http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf
(Accessed Sept 20th 2011)

7. Higgins J. and Green S.
Cochrane Handbook for Systematic Reviews of Interventions (2008)
The Cochrane Collaboration
http://www.cochrane.org/training/cochrane-handbook
(Accessed Sept 1st 2011)

8. Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L, et al
Dapagliflozin a novel SGLT2 inhibitor induces dose-dependent glucosuria in healthy subjects.
Clin. Pharmacol Ther. 2009; 85:520-6

9. Musso G, Gambino R, Cassader M, Pagano G.
A novel approach to control hyperglycaemia in type 2 diabetes: Sodium glucose co-transport (SGLT) inhibitors. Systematic review and meta-analysis of randomised trials
Annals of Medicine, 2011, Early On-line 1-19

Appendix

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]				**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 Inhibitor Vs. metformin**
Aim: Determine if dapagliflozin, lowers HbA1c in type 2 diabetes in patients with inadequate HbA1c control with metformin				
Study Particulars	**Multi Centre:** 81 **Duration of intervention**: 24 weeks **Duration of run in**: 2 weeks **Followup:** on completion of 24 weeks, a 102 week long-term study **Design:** 4-arm RCT, double blind, placebo controlled **Primary outcome:** Change from baseline in HbA1c at week 24 **Secondary outcomes:** At 1 week, change in fasting plasma glucose At 24 weeks changes in: • Fasting plasma • Glucose concentration, • No. with baseline HbA1c of 9% or more. Proportion of patients achieving a therapeutic HbA1c, and Total bodyweight.. Change from baseline in bodyweight, and decreases in bodyweight of 5% or more.			
Participant Criteria	**N:** 534 analysed **Inclusion criteria:** participants aged between 18 years and 77; Type 2 diabetes, BMI <45kg/m2, HbA1c 7-10.0%; fasting C-peptide >0.34ng/ml, taking stable dose metformin>1500mg **Exclusion criteria (taken from paper):** (serum creatinine 133 µmol/L or more for men or 124 µmol/L or more for women (consistent with metformin labeling); urine albumin/creatinine ratio more than 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); and systolic blood pressure 180 mm Hg or more or diastolic blood pressure 110 mm Hg or more. Any significant other systemic disease **Lead in period:** 2 weeks, single blind, to assess compliance with placebo, patients randomised successful completion. Metformin dose stabilised to >1500mg			
Quality	**Study Quality:** medium – See Quality table for further information			
Participant baseline data	**Group 1 (n analysed=134):** Placebo OD + metformin,	**Group 2 (n= 135):** 2.5mg dapagliflozin OD, metformin	**Group 3 (n= 133):** 5mg dapagliflozin OD, metformin	**Group 4 (n= 132):** 10mg dapagliflozin OD,
	Age: 53.7 SD 10.3 years **Sex:** 55% Male **BMI (KG/M^2):** 31.8 SD 5.3 **HbA1c (%):** 8.11% SD 0.96 **Duration of Diabetes:** 5.8 SD 5.1	**Age:** 55.0 SD 9.3 years **Sex:** 51% Male **BMI (KG/M^2):** 31.6 SD 4.8 **HbA1c (%):** 8.96% SD 2.39 **Duration of Diabetes:** 6.0 SD 6.2	**Age:** 54.3 SD 9.4 years **Sex:** 50% Male **BMI (KG/M^2):** 31.4 SD 5.0 **HbA1c (%):** 8.17% SD 1.0 **Duration of Diabetes:** 6.4 SD 5.8	**Age:** 52.7 SD 9.9 years **Sex:** 57% male **BMI (KG/M^2):** 31.2 SD 5.1 **HbA1c (%):** 7.92% SD 0.82 **Duration of Diabetes:** 6.1 SD 5.4

	FPG (mmol/l): 9.19 SD 2.57 **Systolic BP:** 127.7 SD 14.6		**FPG (mmol/l):** 8.96 SD 6.2 **Systolic BP:** 126.6 SD 14.5		**FPG (mmol/l):** 9.39 SD 2.7 **Systolic BP:** 126.9 SD 14.3		**FPG (mmol/l):** 8.66 SD 2.15 **Systolic BP:** 126.0 SD 15.9	
Outcome (change from baseline at study end)								
	Group 1 (n analysed=134): Placebo OD + metformin,		**Group 2 (n= 135):** 2.5mg dapagliflozin OD, metformin		**Group 3 (n= 133):** 5mg dapagliflozin OD, metformin		**Group 4 (n= 132):** 10mg dapagliflozin OD,	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ HbA1c (%)	-0.3	-0.44 to -0.16	-0.67	-0.81 to -0.53	-0.70	-0.85 to -0.56	-0.84	-0.98 to -0.70
Δ Weight (kg)	-0.9	-1.4 to -0.4	-2.2	-2.8 to -1.8	-3.0	-3.5 to -2.6	-2.90	-3.3 to -2.4
Δ FPG (mmol/L)	-0.33	-0.62 to -0.04	-0.99	-1.28 to -0.69	-1.19	-1.49 to -0.90	-1.3	-1.60 to -1.00
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Δ SBP (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	**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):** 2.5mg dapagliflozin OD, metformin		**Group 3 (n= 133):** 5mg dapagliflozin OD, metformin		**Group 4 (n= 132):** 10mg dapagliflozin OD,	
Specific Events	UTI: n= 11, GTI n = 7, HypoT n=1, HypoG n=4,		UTI: n= 6 GTI n = 11 HypoT n=0, HypoG n=3		UTI: n= 10, GTI n = 18 HypoT n=2, HypoG n=5,		UTI: n= 16, GTI n =12, HypoT n=0, HypoG n=5	
	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	
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activties (MedDRA v12.1) via patient questionnaire and active questioning during visits							

Nauck MA, Del Prato S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al **Dapagliflozin Vs Glipizide as Add-on Therapy in Patients with Type 2 diabetes who have inadequate glycaemic control with Metformin** Diabetes care 2011. 34:[2015-2022]		**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 Inhibitor + metformin vs metformin + glipizide**
Aim: Compare efficacy, safety and tolerability of dapagliflozin with glipizide, in patients with type 2 diabetes poorly controlled with monotherapy		
Study Particulars	**Multi Centre:** 95 sites across 10 countries World-wide **Duration of intervention**: 52 weeks **Duration of run in**: 2 weeks **Followup:** on completion of 52 weeks, a 156 week long-term study **Design:** 2-arm parallel group, RCT. **Primary outcome:** Absolute change from baseline in HbA1c at week 52 **Secondary outcomes:** - Change in total body weight - Proportion with hypoglycaemicepisode - Proportion if ≥ 5% total weight loss.	
Participant Criteria	**N:** 801 analysed **Inclusion criteria:** participants aged 18 years and older; inadequately controlled type 2 diabetes, BMI ≤45kg/m2, HbA1c >6.5 and ≤10%; fasting C-peptide ≥0.33nmol/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, fasting plasma glucose ≤15mmol/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 x upper limit of normal; total bilirubin >34 µmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSH; systolic blood pressure ≥180mmHg and/or diastolic blood pressure ≥110 mmHg; significant other disease.	
Interventions	**Intervention 1:** 2.5mg dapagliflozin + metformin **Intervention 2:** 5mg glipizide + metformin **Lead in period:** 2 weeks, single blind placebo lead in prior to randomization. **All groups:** Patients randomly assigned to double blind therapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All patients maintained metformin	
Quality	**Study Quality:** medium – See Quality table for further information	
Participant baseline data	**Group 1** (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin	**Group 2 (**start n= 408, analysed n= 401): 5mg glipizide + metformin
	Age: 58 SD 9 years **Sex:** 55.3% Male **BMI (KG/M^2):** 31.7 SD 5.1 **≥ 25 kg/m^2**: 95%% **≥ 30 kg/m^2:** 57% **HbA1c (%):** 7.7% SD 0.9 **Duration of Diabetes:** 6 SD 5	**Age:** 59 SD 10 years **Sex:** 54.9§% Male **BMI (KG/M^2):** 31.2 SD 5.1 **≥ 25 kg/m^2**: 90.7% **≥ 30 kg/m^2:** 55.4% **HbA1c (%):** 7.7% SD 0.9 **Duration of Diabetes:** 7 SD 6

	FPG (mmol/l): 9.0 SD 2.1		**FPG (mmol/l):** 9.1 SD 2.3	
Outcome (change from baseline at study end)				
	Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin		**Group 2 (**start n= 408, analysed n= 401): 5mg glipizide + metformin	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ HbA1c (%)	-0.52	-0.60 to -0.44	-0.52	-0.60 to -0.44
Δ Weight (kg)	-3.22	-3.56 to -2.87	+1.44	+1.44
Δ FPG (mmol/L)	-1.24	-1.42 to -1.07	-1.04	-1.22 to -0.98
	Mean	**SD**	**Mean**	**SD**
Δ SBP (mmHg)	-4.3	-	-+0.8	-
HbA1c	-	-	-	-
Adverse Events	**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 ≥3%** 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 =*** *n=318* ***Group 2 =*** *n=318* No deaths in Dapagliflozin group 3 deaths in Glipizide group
	Group 1		**Group 2**	
Specific Events	UTI: n=44, GTI n = 50, HypoM n= 0 HypoS n= 7 HypoO, n=7 Events Leading to Discontinuation, n=0		UTI: n=26, GTI n = 11, HypoM n= 3 HypoS n= 147 HypoO, n=40 Events Leading to Discontinuation, n=6	
	Diarrhoea n= 19 Nausea n= 14 Vulvovaginal mycotic infection n= 14 Back pain n= 19 Nasopharyngitis n= 43 Cough n= 15 Influenza n= 30 Pain in extremity 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 Pain in extremity n= 21 Upper resp. Tract Infection n= 17 Headache n= 17 Hypertension n= 35	
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activties (MedDRA v12.1) via patient questionnaire and active questioning during visits			

Rosenstock J, Polidori D, Zhao Y, Sha S, Arbit D, Usiskin K et al. **Canagliflozin, an inhibitor of sodium glucose co-transporter 2, improves glycaemic control, lowers body weight, and improves beta cell function in subjects with type 2 diabetes on background metformin** Diabetologia 2010 53:[S349]	**Funding source:** *Johnson and Johnson* **Placebo + metformin** **vs** **SGLT2 Inhibitor + metformin OD** **Vs** **SGLT2 inhibitor BD + metformin OD** **Vs** **sitaglipitin OD + metformin**
Aim: Assess the safety, tolerability and efficacy of an alternative SGLT2 inhibitor Canagliflozin and remaining beta cell function, in DM type 2 patients who have inadequate glycaemic control using metformin as a monotherapy.	
Study Particulars	**Multi Centre:** no comment in abstract **Duration of intervention**: 12 weeks **Duration of run in**: no comment in abstract **Followup:** no comment in abstract **Design:** 7-arm parallel group, RCT. Double blind, placebo controlled trial looking at metformin, canagliflozin 50, 100, 200, 300mg OD and 300mg BD, and sitaglipitin 100mg **Primary outcome:** Change from baseline in HbA1c and fasting plasma glucose at week 12 **Secondary outcomes:** Assess loss of beta cell function measured using HOMA2-B% derived from plasma glucose and C peptide
Participant Criteria	**N:** 451 analyzed against primary outcome **Inclusion criteria:** People with type 2 diabetes with inadequate glycaemic control using metformin monotherapy **Exclusion criteria (taken from paper):** no comment in abstract **Lead in period:** no comment in abstract
Quality	**Study Quality:** Medium – See Quality table for further information
	7 study groups, each group contained 64-65 patients, individual group numbers not given in abstract Baselines across all groups only given as overall average

Participant baseline data	**Age:** 53 **Sex:** - **BMI (KG/M^2):** 31.5 **HA1c (%):** 7.7% **Duration of Diabetes:** - **FPG (mmol/l):** 9.0 **Systolic BP:** -							
Outcome (change from baseline at study end)								
	Group 1 placebo + metformin		**Group 2** canagliflozin 50mg + Metformin		**Group 3** canagliflozin 100mg + metformin		**Group 4** canagliflozin 200mg + metformin	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ HbA1c (%)	-0.2	-	-0.45	-	-0.51	-	-0.54	-
Δ Weight (kg)	-	-	-1.3	-	-1.5	-	-1.6	-
Δ FPG (mmol/L)	-	-	-0.9	-	-1.4	-	-1.8	-
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Δ SBP (mmHg)	-	-	-	-	-	-	-	-
HbA1c	7.5	0.96	7.2	0.88	7.1	0.85	6.9	0.68
	Group 5 canagliflozin 300mg + metformin		**Group 6** canagliflozin 300mg BD + metformin		**Group 7** sitagliptin + metformin			
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**		
Δ HbA1c (%)	-0.71	-	-0.73	-	-0.56	-		
Δ Weight (kg)	-2.3	-	-2.3	-	+0.4	-		
Δ FPG (mmol/L)	-1.8	-	-1.7	-	-1.0	-		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Δ SBP (mmHg)	-	-	-	-	-	-		
HbA1c	6.8	0.82	6.8	0.72	6.9	0.92		
Adverse Events	***At least one or more adverse event balanced across all arms save for:***							
Specific Events	***Genital tract infections:*** *3-8% canagliflozin arms* *2% placebo* *2% sitagliptin*		***UTI*** *3-9% canagliflozin arms* *6% placebo* *2% sitagliptin*		***Hypoglycaemia*** *(not defined in abstract)* *0-6% canagliflozin arms* *2% placebo* *5% sitagliptin*			

	All AE were seen to be non-dose dependent **After 12 weeks no "safety signals" (not defined in abstract) in lab studies, ECG or vital signs were seen in Canagliflozin arms** **Similar incidences of discontinuation due to adverse events, although number not specified** **Number of severe adverse events not given**
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activties (MedDRA v12.1) via patient questionnaire and active questioning during visits

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 Obes. Metab. 2011 13(10):[928-938]	**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **2.5, 5, 10mg SGLT2 Inhibitor (dapagliflozin) vs 4mg glimepiride**
Aim: To determine 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	
Study Particulars	**Multi Centre:** 84 sites across 7 countries **Duration of intervention**: 52 weeks **Duration of run in**: 2 weeks **Follow-up:** on completion of 52 weeks, a 156 week long-term study **Design:** 2-arm parallel group, double-blind RCT **Primary outcome:** Absolute HbA1c change from baseline to week 24 **Secondary outcomes:** - Total body weight after 24 weeks - Change from baseline after week 24 in post challenge plasma glucose (2hrs) following oral glucose tolerance - Proportion of patients with HBA1c <7% after 24 weeks - Total body weight from baseline if BMI ≥27kg/m^2 • FPG from baseline after 24weeks
Participant Criteria	**N:** 592 analyzed **Inclusion criteria:** Participants aged 18 years and older; inadequately controlled type 2 diabetes, BMI ≤45kg/m^2, HbA1c of ≥7 to ≤10.0%; 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, fasting plasma glucose ≤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 x upper limit of normal; total bilirubin >34 µmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSH; SBP ≥180 mmHg and/or DBP ≥110 mmHg. Any significant other systemic disease							
Interventions	**Intervention 1:** placebo plus 4 mg/day glimepiride **Intervention 2:** 2.5 mg/day dapagliflozin plus 4 mg/day glimepiride **Intervention 3:** 5 mg/day dapagliflozin plus 4 mg/day glimepiride **Intervention 4:** 10 mg/day dapagliflozin plus 4 mg/day glimepiride **Lead in period:** 1 week for inclusion/exclusion review for those switched to 4 mg/day glimepiride **All groups:** dapagliflozin double-blind, glimepiride open label; glimepiride allowed to be down-titrated to 2 mg/day or discontinued in case of hypoglycaemia, no up-titration allowed; in case of inadequate glycaemic control, patients could receive open-label rescue therapy of metformin, pioglitazone or rosiglitazone; all patients received dietary and lifestyle counseling and patients with BMI ≥27 kg/m^2 received advice regarding reducing caloric intake and increasing physical activity							
Quality	**Study Quality:** Medium – See Quality table for further information							
Participant baseline data	**Group 1 (n= 146)** Placebo + glimepiride		**Group 2 (n= 154)** 2.5mg dapagliflozin + glimepiride		**Group 3 (n= 145)** 5mg dapagliflozin + glimepiride		**Group 4 (n= 151)** 10mg dapagliflozin + glimepiride	
	Age (years): 60.3 SD 10.16 **Sex:** 49% male **BMI (kg/m^2)** **≥ 25 kg/m^2**: 86.2% **≥ 30 kg/m^2:** 45.5% **HbA1c (%):** 8.15 SD 0.74 **Duration of diabetes (years):** 7.4SD 5.7 **FPG (mmol/L):** 9.58 SD 2.07 **Systolic BP (mmHg):** 133.3		**Age (years):** 59.9.3 SD 10.14 **Sex:** 50% male **BMI (kg/m^2)** **≥ 25 kg/m^2**: 84.4% **≥ 30 kg/m^2:** 48% **HbA1c (%):** 8.11, SD 0.75 **Duration of diabetes (years):** 7.7 SD 6.0 **FPG (mmol/L):** 9.56, SD 2.13 **Systolic BP (mmHg):** 134.6		**Age (years):** 60.2 SD 9.73 **Sex:** 50% male **BMI (kg/m^2)** **≥ 25 kg/m^2**: 78% **≥ 30 kg/m^2:** 50% **HbA1c (%):** 8.12 SD 0.78 **Duration of diabetes (years):** 7.4 SD 5.7 **FPG (mmol/L):** 9.68 SD 2.12 **Systolic BP (mmHg):** 130.9		**Age (years):** 58.9 SD 8.32 **Sex:** 43.7% male **BMI (kg/m^2)** **≥ 25 kg/m^2**: 79.4% **≥ 30 kg/m^2:** 45.% **HbA1c (%):** 8.07 SD 0.79 **Duration of diabetes (years):** 7.2 SD 5.5 **FPG (mmol/L):** 9.55 SD 2.04 **Systolic BP (mmHg):** 133.8 SD 15	
Outcome (change from baseline at study end)								
	Group 1 (n= 146) Placebo + glimepiride		**Group 2 (n= 154)** 2.5mg dapagliflozin + glimepiride		**Group 3 (n= 145)** 5mg dapagliflozin + glimepiride		**Group 4 (n= 151)** 10mg dapagliflozin + glimepiride	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ from baseline HbA1c (%)	-0.13	-	-0.58	-0.61 to -0.27	-0.63	-0.67 to -0.32	-0.82	-0.86 to -0.51
Δ from baseline Weight (kg)	-0.72	-	-1.18	-1.08 to +0.15	-1.56	-1.47 to -0.21	-2.26	-2.17 to -0.92
Δ from baseline FPG (mmol/L)	-0.33	-	-2.08	-2.50 to -1.00	-1.78	-2.20 to -0.68	-1.94	-2.34 to 0.87

	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Absolute Δ SBP from placebo (mmHg)	-1.20	-	-4.7	-6.1 to -0.9	-4.0	-5.5 to -0.2	-3.8	-6.4 to -1.2
HbA1c	-	-	-	-	-	-	-	-
Adverse Events	**General events – where frequency is ≥3% in any group** UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia				Hypoglycaemia defined as blood sugar <70mg/dl)		***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 2.5mg 1 death in Dapagliflozin 10mg	
	Group 1 (n= 146) Placebo + glimepiride		**Group 2 (n= 154)** 2.5mg dapagliflozin + glimepiride		**Group 3 (n= 145)** 5mg dapagliflozin + glimepiride		**Group 4 (n= 151)** 10mg dapagliflozin + glimepiride	
Specific Events	UTI: n=9, GTI n = 1, ≥ 1Hypo n= 7		UTI: n=6, GTI n = 6, ≥ 1Hypo n= 11		UTI: n=10, GTI n = 9, ≥ 1Hypo n= 11		UTI: n=8, GTI n = 10, ≥ 1Hypo n= 12	
	Bronchitis n= 4 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		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= 4 Hypertension n= 2	
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activties (MedDRA v12.1) via patient questionnaire and active questioning during visits							

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]			**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 Inhibitor + patients own oral antidiabetic drugs (OAD) Vs insulin + OAD**
Aim: Determine if Dapagliflozin, lowers HBA1c in Type 2 diabetes in patients with type 2 diabetes poorly controlled with high insulin doses plus oral antidiabetic agents			
Study Particulars	**Multi Centre:** 26 sites (USA and Canada) **Duration of intervention**: 52 weeks **Duration of run in**: 2 weeks **Followup:** on completion of 52 weeks, a 156 week long-term study **Design:** 2-arm parallel group, RCT **Primary outcome:** Change from baseline in HbA1c at week 12 **Secondary outcomes:** - Change from baseline FPG - Change in total daily requirement of insulin - Percentage of patients with change in HbA1c >0.5% - Percentage of end patients with final HbA1c <7%		
Participant Criteria	**N:** 65 analysed **Inclusion criteria:** Participants aged between 18 years and 75; type 2 diabetes, BMI ≤45 kg/m^2, HbA1c of 7.5-10.0%; taking stable dose metformin (≥1000mg) and/or pioglitazone (≥30mg) for ≥6 weeks and insulin therapy (50 units) ≥12 weeks before enrolment. Fasting C-peptide ≥0.8 ng/ml, serum creatinine <1.5 mg/dl (men) or <1.4 mg/dl (women), and a 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 limits of normal, creatine kinase ≥3 times the upper limits of normal, symptoms of severely uncontrolled diabetes including a history of severe hypoglycemia. Any significant other disease		
Interventions	**Intervention 1:** placebo plus stable dose of insulin sensitizer (metformin and/or pioglitazone) plus insulin (50% of pre-study dose) **Intervention 2:** 10 mg dapagliflozin once daily plus insulin sensitizer and insulin as in intervention 1 **Intervention 3:** 20 mg dapagliflozin once daily plus insulin sensitizer and insulin as in intervention 1 **All groups:** insulin dose reduced to 50%; diet and exercise programme (American Diabetes Association or similar local guidelines); following lead in period there were no dose adjustments to OADs; insulin could be down-titrated in patients at risk of hypoglycaemia **Lead in period:** 10-21 day to establish reduced insulin dose		
Quality	**Study Quality:** Medium – See Quality table for further information		
Participant baseline data	**Group 1 (n analysed=19):** Placebo, OADs + insulin,	**Group 2 (n= 23):** 10mg dapagliflozin, OADs + insulin,	**Group 3 (n= 23):** 20mg dapagliflozin OD, OADs + insulin,

	Age (years): 58.4 SD 6.5 **Sex:** 69.6% male **BMI (kg/m^2):** 34.8 SD 4.6 **HbA1c (%):** 8.40% SD 0.9 **Duration of diabetes (years):** 7.4SD 5.7 **FPG (mmol/L):** 9.22 SD 2.86 **Systolic BP (mmHg): n/a**		**Age (years):** 55.7 SD 9.2 **Sex:** 54.2% male **BMI (kg/m^2):** 35.5 SD 3.6 **HbA1c (%):** 8.4% SD 0.7 **Duration of diabetes (years):** 11.8 SD 5.8 **FPG (mmol/L):** 8.67 SD 2.17 **Systolic BP (mmHg): n/a**		**Age (years):** 56.1 SD 10.6 **Sex:** 54.2% male **BMI (kg/m^2):** 36.2 SD 4.6 **HbA1c (%):**8.5% SD 0.9 **Duration of diabetes (years):** 11.3 SD 5.6 **FPG (mmol/L):** 8.98 SD 3.06 **Systolic BP (mmHg): n/a**	
Outcome (change from baseline at study end)						
	Group 1 (n analysed=19): Placebo, OADs + insulin,		**Group 2 (n= 23):** 10mg dapagliflozin, OADs + insulin,		**Group 3 (n= 23):** 20mg dapagliflozin OD, OADs + insulin,	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ HbA1c (%)	+0.09	-0.2 to +0.4	-0.61	-0.9 to -0.4	-0.69	-0.90 to -0.4
Δ Weight (kg)	-1.9	-2.9 to -0.9	-4.50	-5.5 to -3.5	-4.3	-5.3 to -3.3
Δ FPG (mmol/L)	+0.99	+0.08 to +1.90	-0.13	-0.75 to +1.02	-0.53	-1.42 to +0.35
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Δ SBP (mmHg)	-	-	-7.2	-	-6.10	-
HbA1c	8.5	0.8	7.80	0.7	7.80	0.60
Adverse Events	**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=15* ***Group 2 =*** *n=18* ***Group 3 =*** *n=16* *One patient in each group discontinued due to adverse effects*	
Specific Events	**Group 1 (n analysed=19):** Placebo, OADs + insulin,		**Group 2 (n= 23):** 10mg dapagliflozin, OADs + insulin,		**Group 3 (n= 23):** 20mg dapagliflozin OD, OADs + insulin,	
	UTI: n=0, GTI n = 1, HypoT n=n/a, HypoG n=3		UTI: n= 0, GTI n = 0, HypoT n=n/a, HypoG n=7,		UTI: n= 1, GTI n = 5, HypoT n=n/a, HypoG n=6	
	Nausea n= 1 Pollakiuria n= 4 Back pain n= 2 Nasopharyngitis n= 2 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 odema n=2 Abdominal pain n=2 Fatigue n= 1 Influenza n= 1 Pain in extremity n= 1 Upper resp. Tract Infection n= 1	

Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activties (MedDRA v12.1) via patient questionnaire and active questioning during visits

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	no
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3 to 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	tables
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7

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Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	tables
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	tables
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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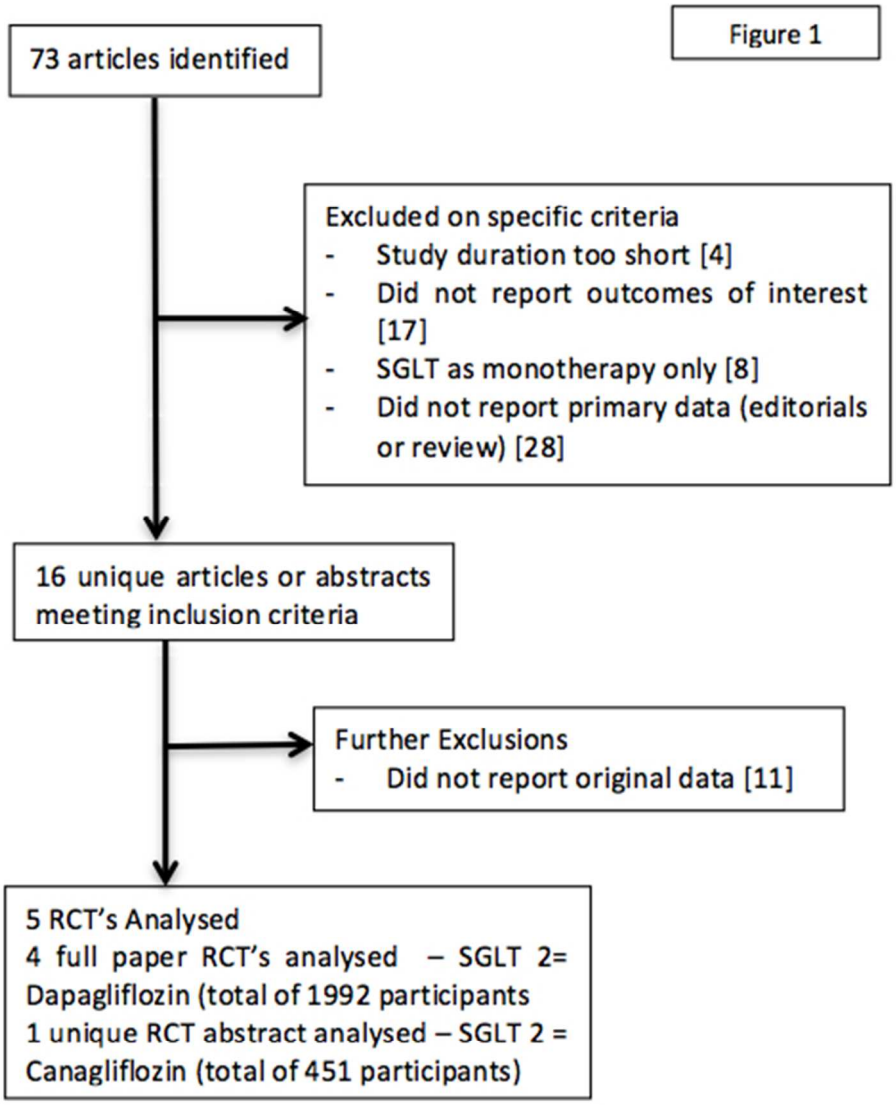
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.



Results of literature search, and exclusions at each stage

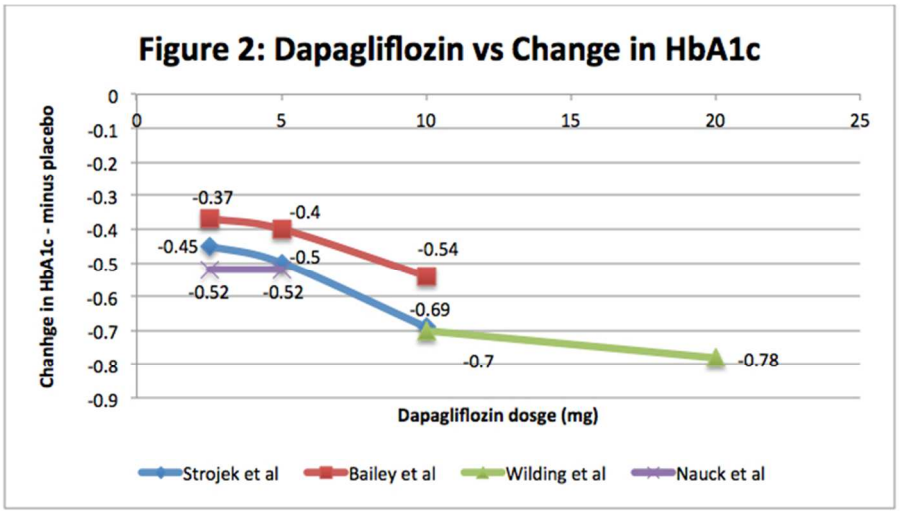
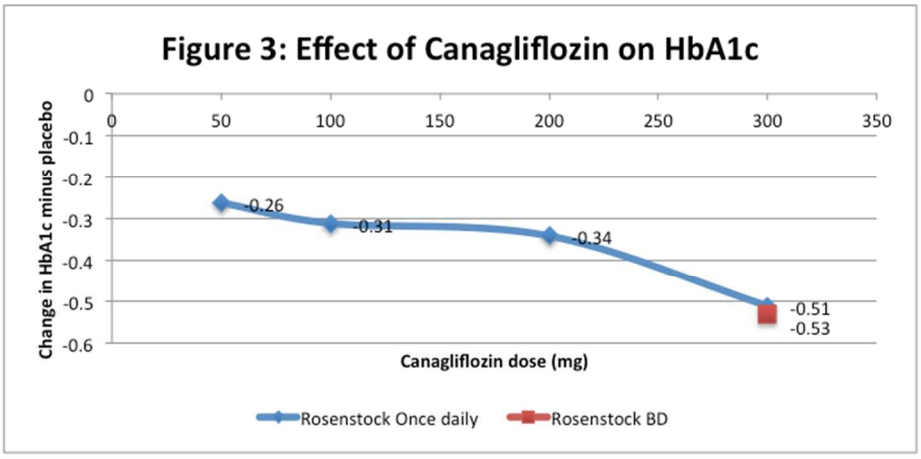
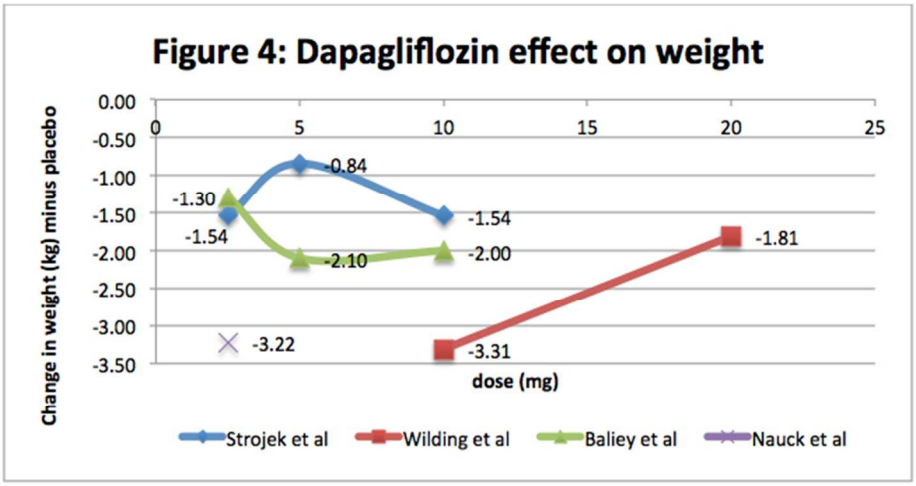


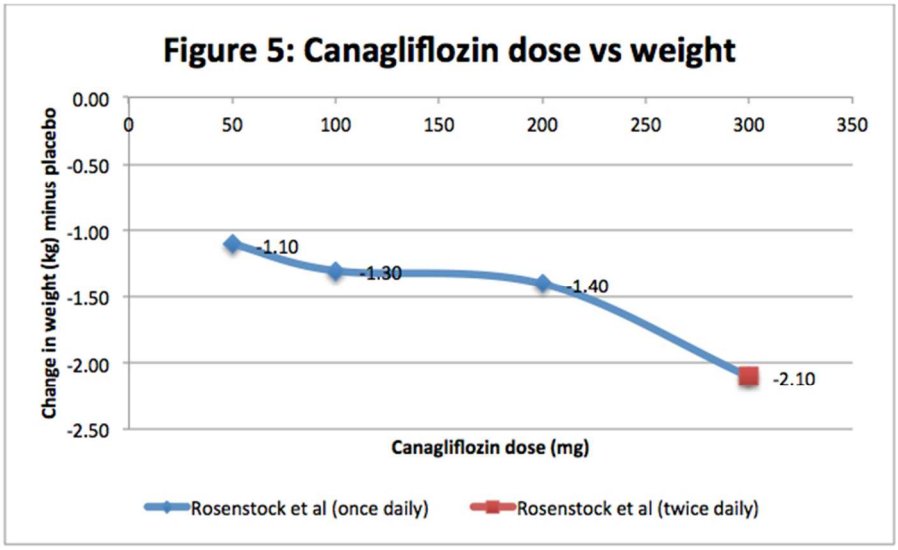
Figure showing reduction in HbA1c due to Dapagliflozin,



Showing reduction in HbA1c due to canagliflozin, of note is that twice daily administration has no significant effect compared to once daily at the 300mg dose



Effect on weight due to dapagliflozin compared to that of placebo



Effect of canagliflozin on weight compared to placebo

Systematic Review of SGLT2 Receptor Inhibitors in dual or triple therapy in type 2 diabetes

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001007.R1
Article Type:	Research
Date Submitted by the Author:	18-Apr-2012
Complete List of Authors:	Gill, James; University of Wariwick, Division of Health Sciences; University Hospitals Coventry and Warwickshire, Endocrinology Clar, Christine Waugh, Norman; Warwick University, Division of Health Sciences Court, Rachel; Warwick University, Division of Health Sciences
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics, Evidence based practice
Keywords:	DIABETES & ENDOCRINOLOGY, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY

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Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	no
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3 to 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
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Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-11
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Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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For more information, visit: **www.prisma-statement.org**.

Dapifloz peer review responses

Reviewer 1	
Written english is okay bit they did a ton of bullets that should be changed. Again, mentioned this in comments to authors.	
Major comments	
Overall comments: This is a systematic review discussing the SGTL2 receptor inhibitors used as combination therapy for treatment of type 2 diabetes. While this is an important topic as we need to know what is the best 2nd and 3rd line agent for type 2 diabetes, the article is limited in the lack of trials to include in this systematic review which make it tough to draw many conclusions regarding safety outcomes. In addition, only one of the studies is an active comparator while the rest are placebo controlled trials making the data less useful since we can't determine the comparisons between adding januvia versus an SGLT2 inhibitor for instance based on the data available. However, it does provide information on the general efficacy of SGLT2 inhibitors when used as combination therapy.	Fair points, but we can only report what research there is. And it is not correct that only one trial had an active comparator – there were two active comparators, glipizide in Nauck 2011 and sitagliptin in Rosenstock 2010.
1) The introduction needs to address why this topic needed a systematic review. i.e. Few people know about the potential benefits or harms of SGTL2 inhibitors used as dual or triple combination therapy for type 2 diabetes; therefore, we decided to conduct as systematic review of SGTL2 inhibitors to assess the efficacy and safety of these agents used as combination therapy for adults with type 2 diabetes. Would add safety not just efficacy into all statements where you say you are assessing efficacy since you do also	Section added at end of Introduction with similar message to referee's comments, and mentioning safety.

assess safety in your results.	
2) The appendix table is okay but is so big and long that it does not provide a great summary of the articles within one viewing segment. I would recommend another summary table showing key aspects of the study so that all 5 articles can be viewed on one page listing in columns: N of participants, dose of drug in each arm and names of drugs in each arm can be listed as rows under each study, mean baseline a1c, mean age, gender, key inclusion/exclusion criteria, country of study, study quality, and change in a1c between groups (which can be calculated) and whether statistically significant differences between groups or not.	A summary table with all the variables suggested by the referee would be rather large, but we take the point that a summary table would be useful. We have inserted one which is not quite as extensive as he suggested.
3) The discussion talks about the lack of long term data on safety and long term outcomes but does not mention the potential safety concerns of cancer, liver toxicity, and nephropathy. These were brought up in the FDA review of the drug and was why it was not yet FDA approved. I think it is reasonable to mention these issues to the reader and note that we need further studies specifically in these areas to address potential concerns of specific adverse effects.	We have added a paragraph on the FDA review.
4) I found the article results difficult to follow since there was no range in mean differences between groups. This could probably be helped by either putting that in the text or adding the summary table to the article as discussed in #2.	Table added
Minor issues	
1) Abstract background: consider adding at the end of the sentence “, and little is known regarding their efficacy and safety when used as dual or triple therapy for type 2 diabetes.” This will help make it	We have added some text to the Objective in the Abstract to make it clear that our review is about the use of these drugs in dual or triple therapy.

more clear to the reader why a systematic review needs to be conducted.	
2) Abstract objective: consider adding "and safety" after effectiveness. May want to change effectiveness to efficacy since data are all from RCTs which are mainly efficacy trials not effectiveness trials done in the "real world".	Safety added.
3) Abstract Inclusion criteria: consider adding randomized before the word trials.	We have added "randomised controlled"
4) Abstract Results: Seems like you could put the range in between group differences for a1c and weight loss for the placebo controlled trials here. Also, trial quality appeared good does not sound scientific. You used a validated instrument to assess risk of bias-why not provide the quantitative results of that assessment in results.	Figures for HbA1c changes added to Abstract. No change to "good quality" – it's a standard expression in systematic reviews. Text on safety added to Abstract.
5) Globally, I have never seen an article use so much bulleting before. One problem with bulleting is you feel a bit like you are reading an outline in some parts as opposed to a written article. Please fix that throughout unless the editor states differently. I would write it as a sentence with commas wherever this occurred.	We don't think the use of bullets is excessive but will amend it if the editor wishes.
6) I also found it hard to follow the headers since I am so used to articles being laid out in specific ways. (i.e. background, methods, results, and discussion). Usually, I only see subheadings under methods and results. I thought the subheadings in the background should be removed (i.e. subheading decision problem and review objectives – can keep text under subheadings just do not need the subheadings in my opinion – I found it	We have amended the structure slightly by having bolder headings for Introduction, Methods, Results, Discussion. We have removed the subheading on objectives, and the sentence that followed it, from the Introduction, and have expanded the preceding paragraph. However we have kept the subheadings in Methods and Results.

confusing), and under methods need to make less subheadings - could divide into 3 sections: data sources and selection (include search strategy, inclusion/exclusion criteria here), data extraction and quality assessment, and data synthesis and analysis.	
7) Would add rationale for systematic review as mentioned under major issues above prior to subheading listed as review objectives.	Done
8) Would consider removing the sentence under decision problem that states we start from the position that the first line drug in type 2 diabetes is metfromin… Although I agree that these meds are unlikely to replace metformin, you do not need the sentence since will state rationale for why you are looking at it in combination therapy. You could add a sentence earlier instead when talking about rationale for not looking at it in monotherapy by stating that a recent systematic review has already evaluated the class as monotherapy.	Paragraph removed – having expanded what is now the last paragraph of the Introduction, we no longer need the "Decision problem" section. Sentence added.
9) Above participants on page 3, delete the two sentences above participants which discuss outcomes and looking at trials against placebo since this should be and is under methods already. Redundent and does not need to be here.	We have removed the sentence on outcomes, since those appear in the Methods section. However since Questions 1 and 2 focus on active comparators, we think it is worth retaining the sentence on placebo trials. We have reduced the length of this section by amalgamating questions 1 and 2.
10) Would start methods before study participants and all the following information should be put without bullets under one of the three headings mentioned above.	Methods now starts as suggested. Subheadings retained
11) Would remove all times when you state "if data permitted". You are just describing methods here. In results, you can state that there were no data to answer a specific question.	Done

12) In methods when you describe looking at subgroups, would consider removing the categories of duration. Not needed really. Just use the statement that you already have regarding exploring duration of diabetes.	Categories retained because this was to address a specific hypothesis
13) Report methods for synthesis of evidence of clinical effectiveness. I would move this sentence to right above your discussion of data synthesis and add the words "to be described in detail below".	OK, done, and subheading removed.
14) Study selection: would add the words inclusion/exclusion before the word criteria for clarity.	OK, done
15) I could not tell if the quality assessment was done independently by 2 reviewers. The word verified should be changed if it was done independently as verified makes me think someone only looked over someone's else's answers in which case it would be a serial not an independent review.	Changed from "independently verified" to "checked".
16) Usually the Figure 1 has two boxes above the one listed there. One box shows all sources of data and N of titles reviewed (i.e. medline N=12000, handsearch N=29, embase N=13000 with an N excluded between title and abstract review. A second box listing N abstracts reviews would come above N full articles reviewed with an arrow to the side listing N of exclusions. Usually there are some reasons for exclusion listed between abstract and full article review boxes – would add that here if available. Would also remove fig 1 from box and have as a title. "Figure 1: Study flow diagram" or Figure 1: literature search results could be used for instance.	The sources of data are in the text. Title of figure amended and text below moved to start of Results.
17) Would move results header to above the	Results heading moved, but most subheadings

sentence on literature search results. Would remove subheaders of participants, interventions, leadin periods, and power. Would consider replacing with one heading called study characteristics and quality or could have study characteristics followed by quality then rest of headers as is. Power paragraph should go under a more global assessment of quality. You provide the quality table but only discuss power in the text. Would choose a few key issues such as allocation concealment and total dropout from the table to discuss in the text as one quality paragraph total.	retained.
18) Would change figure 2 header to change in a1c by dapagliflozin dose.	Done
19) If able, would be useful to have standard error bars in figures 2 through 5	Some figures removed
20) Under SBP, mention if compared to placebo here so it is obvious to the reader. Would make sure that is clear for all results.	Fair point. Text added to clarify.
21) It was not clear from the article that dapagliflozin reduces SBP based on 2 articles. In discussion, could say that it may also reduce SBP but need more data to further substantiate this or please make more evident why you think this is true. I did not feel that two RCTs with small differences in one of them was sufficient to say with certainty and unclear from results if the -2.7 was statistically significant.	All four dapagliflozin trials reported SBP reductions.
22) In discussion, you list SGLT2 inhibitors under nine classes. Are these available for use in Canada? If so, keep here. If not, may want to point out that the other 8 classes are available for use and that this class is not yet approved for use in all	Being based in the UK, we don't know what is available in Canada. All the other 8 classes are available in the UK, and dapagliflozin is expected to be submitted for licensing soon.

countries.	
23) Limitations – you state wilder noted one case of renail failure. Seems like that should also be listed under adverse events section under results.	Ok, moved to Adverse events section
24) Statement about wilder matching by demographics but could be biased by differences in prior med use seemed a bit strange. If this was an RCT, then shouldn't the background meds have been similar between groups? Was it not?	Fair point. Sentence deleted.
25) Usually I see ceiling of effectiveness written as ceiling effect but that is in the US. If the Canadian terms are different, then leave as is. If not, then would change to ceiling effect.	No change. There could be ceiling effects in adverse events too
26) In discussion, you state that UTIs were only mild infections not requiring treatment. May be worth adding a statement afterward that we need more studies with more people to have sufficient power to determine if there were differences in more serious UTIs requiring treatment.	OK, text revised and we have added the figures from Nauck, the largest study and calculated percentages and CIs.
27) In conclusions, you state that SGLT2 inhibitors appear safe as much as can be assessed via short term trials. I would probably take the safe part out here – you could comment on the hypoglycemia effect if you want. You could state that they are effective at reducing a1c and weight. I would add a sentence stating that we can not be sure of its impact on long term outcomes or safety until long term large studies are conducted assessing both long term outcomes and rare adverse events such as cancer, renal failure, and liver toxicity among others.	Safe bit removed and paragraph on FDA review added.
28) Abstract conclusion – would remove safe	Done.

from the sentence and would state effective at reducing a1c and weight in short term RCTs.	
Reviewer 2 Jennifer Hirst	
Presentation of results in the abstract is too brief and and needs to provide an answer to the research questions	Abstract is already close to word limit.
Text in search methods states that 344 hits were returned from searches whereas Figure 1, the Flow chart only begins with 73 articles. Nowhere in the text is this discrepancy clarified.	Figure 1 revised to clarify this
A description of the statistical methods needs to be given.	None used.
On page 6 details of study participants are presented, with numbers in brackets, it needs to be made clear whether these numbers represent the range or confidence intervals.	Clarified by addition of “range”
References for all the included studies should be included in the reference list.	Done
Written presentation: Page 6 - Lead in periods - wording in the last sentence is unclear: "Only in the Rosenstock..."	Revised
Page 8 Body Weight - the first sentence extends to 6 lines and needs breaking into at least 3 sentences.	Revised
Page 8 last sentence - not clear what the message is here.	That weight loss in trials may be due to being in the trial not due to the drugs.
Appendix. One of the studies in the table (Rosenstock) has no details of number of participants	The total number is given.
Appendix: pages 15 and 16 - Group 4 -10mg dapagliflozin - is this in combination with metformin? If not, then it does not meet the	Yes is in combination with metformin – added to box.

inclusion criteria.	
The results of this systematic review have been presented in graphical format, with data points from all included studies plotted together. In this format it is difficult to interpret the data, though the authors have attempted to do this through narrative and overall statements. The authors state that a meta-analysis was not conducted because of the small number and heterogeneity of the trials. As 5 trials have been included in the review, and each of these report outcomes which can be compared, a meta-analysis could be conducted. The authors throughout the paper make summary statements about the results, however the method of analysis used by the investigators is not appropriate to draw these conclusions. A meta-analysis should be conducted and would substantially improve the paper.	A meta-analysis would have been entirely inappropriate because of the heterogeneity of the studies. No – a meta-analysis should not be done. You can't combine a study of triple therapy with others of dual, or one of canaglifozin with some of dapagliflozin, or studies with different comparators.
A table summarising the study characteristics of included studies is needed in the results section. Suggest to include details of intervention & comparator medications, numbers of participants in each arm, dose and length of study.	Table added with the arms of most interest.
The curved line connecting the points on the graphs implies that the trend has been observed. As this is not the case, a straight line or preferably a dotted line would be more appropriate. In addition, confidence intervals should be provided on the graphs, with data points being slightly offset so confidence intervals can be seen.	Lines removed.
Results - 1st paragraph - in the text report SGLT2 inhibitors to lower HbA1c by between -0.52 and -0.78%, but Figure 2 shows this to be	Corrected.

between -0.37 and -0.78%	
-2nd paragraph - "no difference ... between dapagliflozin and glipizide" - Figure 2 appears to show a comparison of 2.5mg and 5mg. It is misleading to present data from an arm of the trial without dapagliflozin in this graph.	Accepted, and glipizide cross removed
There is no discussion of Figure 3 or Figure 5	Figure 3 now discussed. Figures 4 and 5 removed
Body weight - median weight reduction of -2.33kg presented with confidence intervals. Is this mean rather than median? How was this calculation perfomed and which statistical package was used to get to this value? This value should be obtained using meta-analysis.	Figures were as calculated in original studies. No meta-analysis should be done.
Significant reductions in weight, blood pressure and FPG reported without supporting statistics (means and confidence intervals).	
Hypoglycaemic - "a small but not significantly significant increase in ..... hypoglycaemia across 3 of the 4 studies" - The way the data is presented makes it difficult to judge whether hypoglycaemia is an issue. A meta-analysis of this data is needed to clarify this.	No change
Page 11 - 3rd paragraph. - "optimum dosage ...between 10-20mg" - of your 5 trials, there was only 1 trial which used a dose of over 10mg, and this was the smallest of the included trials with a maximum of 23 patients in each arm. No confidence intervals are presented, it is therefore not possible to say whether the observed difference at 20mg is significantly different from that at 10mg. There is insufficient evidence presented to conclude that an	Fair point, and paragraph replaced with new one.

optimum dosage of 10-20mg.	
The presentation of the results in this review needs to be revised. This could be achieved by conducting a meta-analysis. Data could then be presented in subgroups of dose. A summary statistic estimate need not be presented particularly if heterogeneity is large, but should be considered. The authors are strongly urged to conduct a meta-analysis of their data.	We remain convinced that a meta-analysis would not be appropriate.

Title: 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: four trials, published in full, assessed dapagliflozin and one, only available as a conference abstract, assessed canagliflozin. Trial quality appeared good for the published trials, however it could not be assessed for the conference abstract. Dapagliflozin reduced HbA1c, by 0.54% to 0.7% compared to placebo, but there was no difference compared to glipizide. Canagliflozin reduced HbA1c slightly more than sitagliptin (reductions of 0.71% and 0.56%). Both dapagliflozin and canagliflozin led to weight loss.
Limitations: trials were short term. No breakdown of relative effectiveness by duration was available. Data on canagliflozin is currently available from only one abstract. Costs of the drugs are not known so cost-effectiveness cannot be assessed. More data on safety are needed, with the FDA 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.

Introduction

Type 2 diabetes is one of the most important and prevalent chronic diseases today, with in 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 (NICE), recommend that if lifestyle intervention is insufficient, the first line of drug treatment is metformin, followed by a sulphonylurea, or sometimes a glitazone, before commencing 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 anti-diabetic medications need to not only 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 (160-180mg/dl) has been reached. At this threshold the proximal tubule cannot reabsorb all of the filtered glucose, resulting in glycosuria. 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 to 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, also 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 SGLT-2 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 the current NICE guideline pharmacological interventions, when prescribed in dual therapy, e.g. metformin plus SGLT2 versus metformin plus sulphonylurea, and in triple therapy, e.g. metformin, sulphonylurea and SGLT2 inhibitor versus metformin, sulphonylurea and dipeptidyl peptidase 4 inhibitors (DPP4) such as sitagliptin

We also look at 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 Cochrane Handbook for Systematic Reviews of Intervention (6)

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 longer than 10 years

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

Interventions:

- Any use of SGLT2 inhibitors in dual or triple therapy, in addition to other interventions including, but not restricted to: sulphonylureas, insulin and gliptins.

Outcome measures.

The outcomes sought were:

- Glycaemic control as reflected in HbA1c – taken as the main outcome of interest
- Change in weight (Kg) or body mass index
- Adverse effects, including hypoglycaemia, UTI and change in quality of life
- Cardiovascular events

Study Design

Randomised control trials (RCT) and systematic reviews of trials are used for 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 to be detected in HbA1c levels due to turnover of red blood cells.

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

Search methods for identification of studies

We searched the following sources:

- MEDLINE
- MEDLINE in-Process
- EMBASE
- The Cochrane Library, all sections
- NHS HTA

- Science Citation Index Expanded (SCI expanded)
- On-going Trials Registers:
- Clinical trials (www.clinicaltrials.gov)
- Current Control Trials (www.controlled-**trials**.com/)
- American Diabetes Association – Conference Abstracts
- EASD – 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. Initially returning 344 hits after the removal of duplications. 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. SGLT-2 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.

Data collection and analysis

Study Selection: two reviewers using the defined inclusion and exclusions criteria above selected studies independently. 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.

The quality of the individual studies was assessed by one reviewer using the Cochrane Risk of Bias score (6) and checked by a second reviewer. Any disagreements were resolved by discussion.

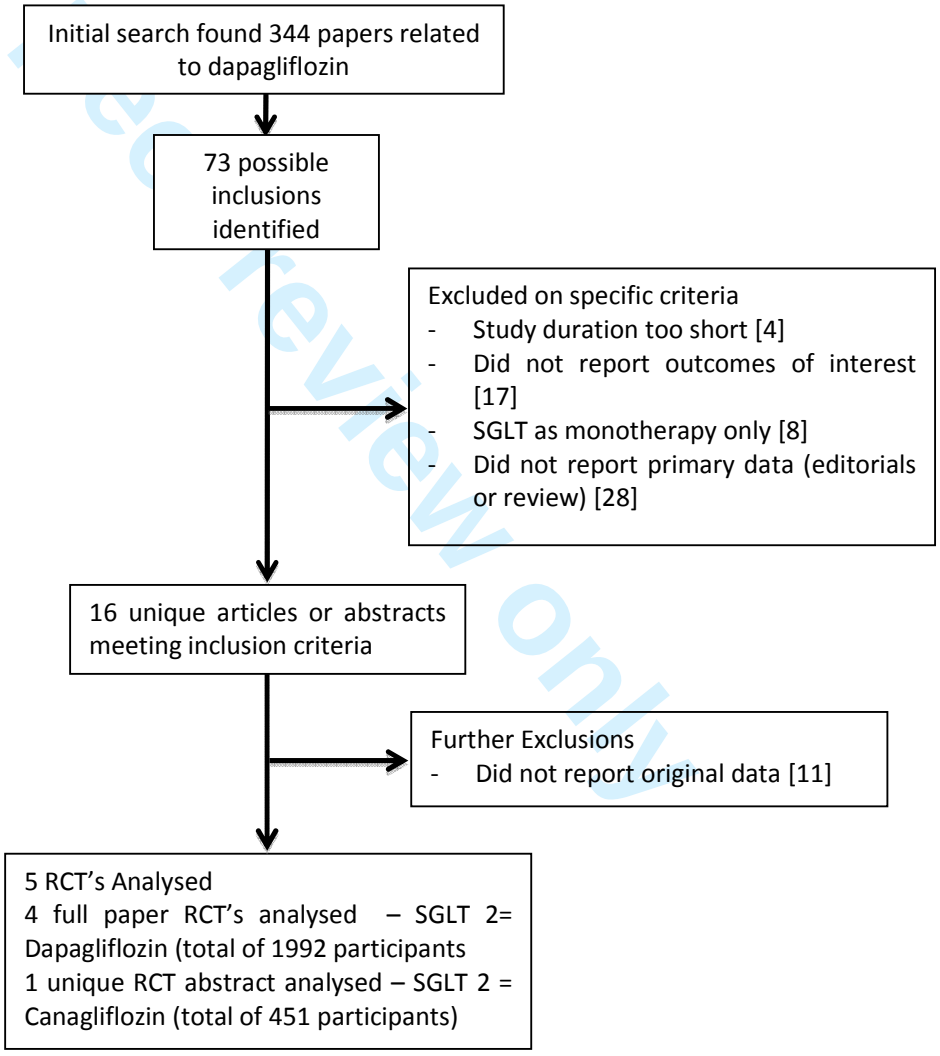
Data synthesis and analysis

This data analysis has been reported according to the guide set down within the Cochrane Handbook for Systematic Reviews of Interventions (6). No meta-analysis was possible due to the small number and heterogeneity of trials.

Results

The results of the literature search are shown in figure 1. After exclusions, made according to the study protocol, 4 RCTs published in full and 1 RCT available as an abstract, in all covering 20 different comparisons remained for analysis.

Figure 1: search results:



The studies are summarised in table 1

Table 1: Summary of trials (selected arms only) and change in HbA1c.

Study	SGLT2 inhibitor	Comparator	Baseline HbA1c	Change in HbA1c	Difference
Bailey 2010 (8)	dapaglifozin 10mg + metformin	Placebo + metformin	dap 7.9% pbo 8.0%	- 0.84% - 0.3%	0.54%
Nauck 2011 (9)	dapagliflozin 2.5mg + metformin	glipizide 5mg + metformin	dap 7.7% glip 7.7%	- 0.52% - 0.52%	No difference
Rosenstock 2010 (10)	canagliflozin 300mg once daily	sitagliptin	can 7.7% sita 7.7%	- 0.71% - 0.56%	0.15%
Strojek 2011 (11)	dapaglifozin 10mg + glimepiride 4mg	glimepiride 4mg + placebo	dap 8.07% pbo 8.15%	- 0.82% - 0.13%	0.69%
Wilding 2009 (12)	dapaglifozin 10mg+ insulin + metformin or pioglitazone	Placebo + insulin + metformin or pioglitazone	dap 8.4% pbo 8.4%	- 0.61% + 0.09%	0.7%

Study participants

Four RCTs (8,9,11,12) assessed dapagliflozin. 1,992 participants received dapagliflozin in total; across four RCTs, with trial durations ranging from 12 to 54 weeks. In the single canagliflozin (10) trial, 451 participants received that drug for 12 weeks.

The median base-line HbA1c across the study populations was 8.14% (range 7.7-9.0%), median BMI of 32.7kg/m^2 (range 31.2 – 36.27kg/m^2) and median age of 56.2yrs (range 53 – 59.9yrs).

Interventions

Dapagliflozin was administered orally, with dose ranges from 2.5mg to 20mg, used as once daily preparations.

Canagliflozin dose ranged from 50mg to 300mg administered once daily, with an additional 300mg group administered twice daily.

Background glucose-lowering drugs included insulin, glimepiride, thiazolidinedione (TZD), metformin and insulin, in combination or singly.

Lead in periods

In two studies, (Nauck and Bailey, 8,9) the metformin dose was stabilised during a 2-week lead in period. Strojek (11) stabilised glimepiride over an 8-week lead in.

Wilding (2009) stabilised all OADs over a 10-21 day run in, before fixing doses for the remainder of the study.

The Rosenstock (2011)(10) abstract on canagliflozin provided no information on pre-study stabilisation of metformin.

Power

All studies included sample size calculations indicating that sufficient numbers of patients were recruited and included in order to detect a 0.5% difference in HbA1c. The Nauck (2011) trial was able to detect 0.35% difference.

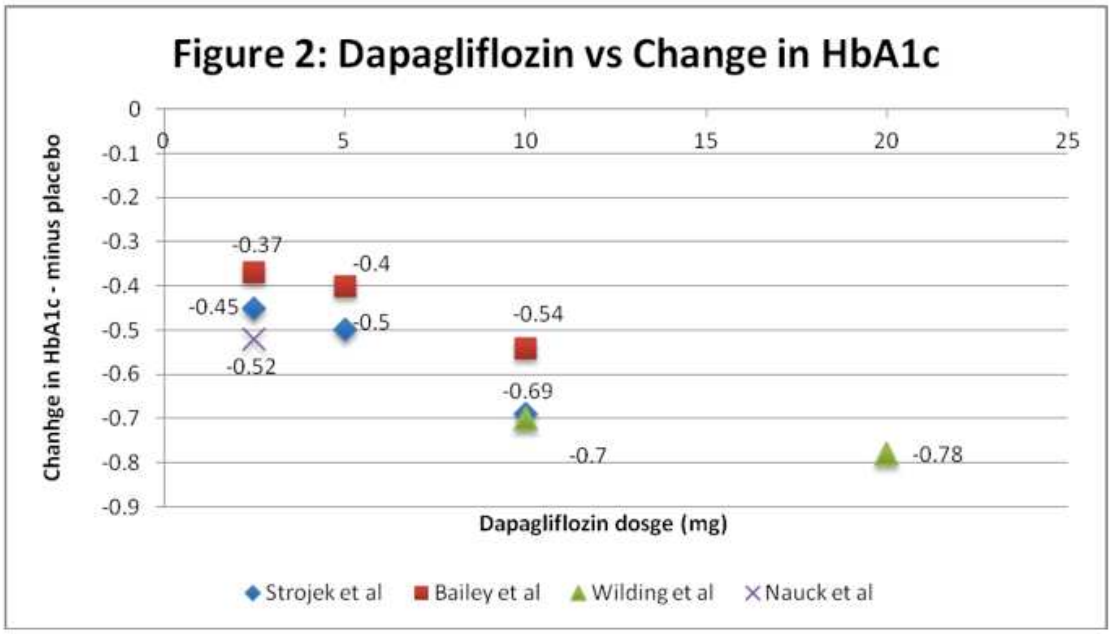
Table 2: Study Quality

Study	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
Bailey 2010	Yes	Yes (double-blind)	Yes – Last record carried forwards	12%	Yes	Yes	Yes – 0.5% difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Nauck 2011	Yes	Yes (Double Blinding and double dummy)	Yes – Last record carried forwards	22.1%	Yes	Yes	Yes - – 0.35% difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Rosenstock 2010	Not reported	Yes (double blinding	Not reported	Not reported	Unclear	Yes	No comment on sample size calculation	*Johnson and Johnson*
Strojek 2011	Yes	Yes (Double Blinding and double dummy)	Yes – Last record carried forwards	8.5%	Yes	Yes	Yes – 0.5% difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Wilding 2009	Not reported	Single blind during lead in, double blind during study	Yes – Last record carried forwards	7.0%	Yes	Partially. Matched for patient demographics, not for prior medications	Yes – 0.5% difference detectable	Astra-Zeneca and Bristol-Myers-Squibb

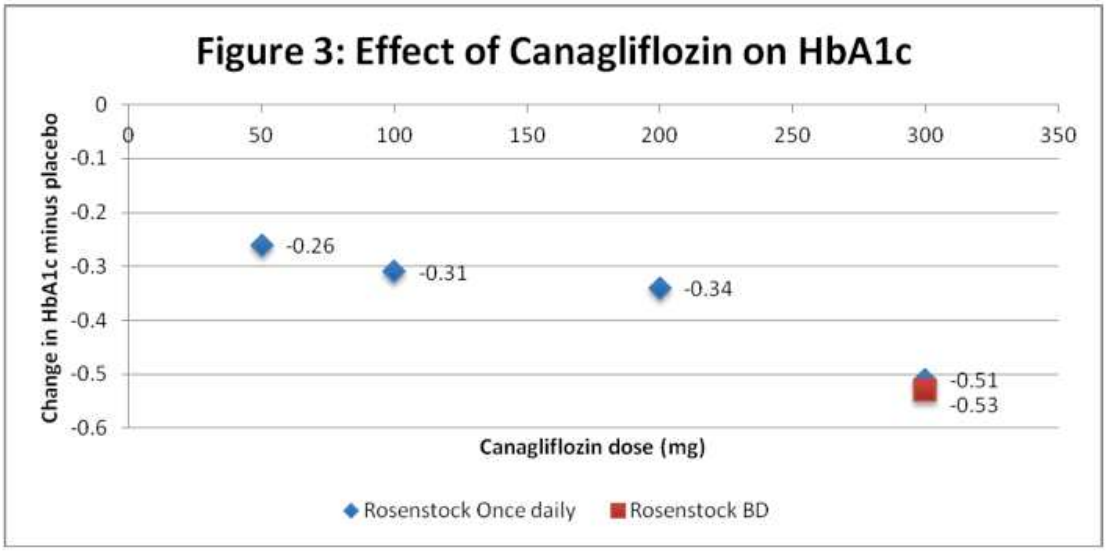
HbA1c Levels

Figure 2 shows change in HbA1c (%) across different SGLT2 inhibitor doses, dapagliflozin from Strojek (2011), Nauck (2011), Bailey (2010) and Wilding (2009). Rosenstock (2010) shows the effect of canagliflozin doses on HbA1c (Figure 3)

Dapagliflozin was shown, as in Fig 2, to reduce HbA1c by between 0.37% and 0.78% when adjusted for changes see by placebo. There was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by 0.52% (Nauck 2011).



Canagliflozin reduced Hba1c in a dose–related manner up to 300mg once daily, with no further reduction seen with a twice daily dose regime, as shown in figure 3.



Weight

SGLT2 inhibitors were associated with a significant difference in the change of weight, with a median weight reduction of -2.33kg (95% CI: -1.19 to -4.50), with the greatest reduction reported by Wilding (2009), of -4.50 kg with 10mg dapagliflozin compared to a reduction of +1.9kg on placebo. The lowest reduction due to SGLT2 was reported by Strojek, of -0.84kg with 5mg dapagliflozin.

Minor reductions in weight were reported for some comparators; OAD + insulin + placebo (-1.9kg); glimepiride + placebo (-0.72Kg, metformin alone (-0.9kg), however some of these effects were probably as a result of the trial effect, rather than a direct effect of the comparator drugs.

The abstract for Rosenstock (2010) suggests that for weight change, there was no difference between canagliflozin 300mg once daily and twice daily.

Wilding (2009) also recorded waist circumferences during the study, finding on average, a reduction of -1.7cm, -2.7 and -2.5cm in 2.5mg, 5mg and 10mg dapagliflozin groups, compared to -1.3cm in the placebo.

Systolic Blood Pressure

In placebo-controlled trials, dapagliflozin produced a significant reduction in systolic blood pressure at all doses, with an effect covering a range from -2.1 mmHg to -7.2 mmHg, compared to reductions of 0.2 to 1.2mmHg for placebo. The greatest reduction (-6.1mmHg) was reported by Wilding (2009) from dapagliflozin 10mg, but it should be noted that there were also changes in insulin dosage at this level. Rosenstock (2010) did not report changes in systolic blood pressure with canagliflozin.

Fasting Plasma Glucose (FPG)

A significant change in FPG was seen in all dapagliflozin groups compared to placebo, with a range of -0.13 to -1.58 mmol/L (unadjusted for placebo) for SGLT2 inhibitors against +0.09 to -0.33mmol/L range for placebo, allowing a maximum reduction of -1.25 mmol/L to be attributed to 10mg dapagliflozin when given as an addition to glimepiride demonstrated by Strojek (2011).

The reductions in FPG rose with SGLT2 dosage; as seen above with the 10mg dapagliflozin dose. Rosenstock (2010) further supported this by showing reductions in FPG from -0.9 to -1.8mmol/l across the 50 to 300mg canagliflozin dosage range, but with no increase in effect above 200mg once daily, indicating a ceiling of efficacy.

Adverse events

Urinary and genital tract infection

Nauck (2011) reported a significant increase in both UTI and genital tract infection (GTI) in the dapagliflozin (2.5mg) group – 44 UTIs and 50 GTIs, (10.8% and 12.3% respectively) compared to glipizide (UTI 26, GTI 11) (6.3% and 2.6%). Amongst the other studies reviewed here, no other significant increase in UTI or GTI was seen. Bailey (2010) suggests that there is no dose related effect in terms of incidence of UTI and GTI for dapagliflozin, demonstrating no difference between dapagliflozin and placebo, with (11/7) (8.20/5.22%) UTI/GTI cases respectively for placebo vs 2.5mg, (6/11) (4.4/8.1%), 5mg ((5/18) (3.75/13.53%)) and 10mg (5/12) (3.78/9.0%). Wilding (2009) similarly reports few infections, with placebo (0 and 1 (4.3%)), 5mg (0 and 0) and finally 20mg ((1/5) (4.3/21.7%)). When reported, UTI and GTIs were not severe and resolved with simple treatment.

Hypoglycaemia

Compared to placebo, dapagliflozin resulted in a small, but not statistically significant, increase in incidence of all forms of hypoglycaemia across three of the four dapagliflozin studies. Hypoglycaemia, where data permitted, was divided into three categories: severe, moderate and other, corresponding respectively to capillary glucose readings of; <3.0Mmol/L, <3.5<Mmol/L, and ”Symptoms suggestive of hypoglycaemia, but without confirming capillary glucose measurement”. The incidence of all forms hypoglycaemia

ranged from 2.2% (Bailey 2010 with 2.5mg dapagliflozin and metformin) to 30.4%. (Wilding 2009, 10mg dapagliflozin + OAD + insulin).

Wilding (2009), 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. Strojek reported a small, dose independent, increase in hypoglycaemia from dapagliflozin 2.5mg, 5mg and 10mg, 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 amongst 592 participants.

Nauck (2011) 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 150 events).

Other Adverse Events

Across all studies, two deaths were reported in dapagliflozin groups, both by Strojek (2011), attributed to cardiopulmonary arrest, and pulmonary embolism after ischaemic stroke respectively. Neither event was considered to be the result of the study medication.
Three deaths were also reported by Nauck (2011) in the glipizide placebo group, none in the SGLT2 group.
Wilding (2009) noted one occurrence of renal failure reported in the dapagliflozin group

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:

i) Reducing HbA1c
ii) Improving weight loss in conjunction with advice on lifestyle and diet
iii) Lowering systolic blood pressure
iv) Decreasing FPG levels

Given the mechanism of action of the SGLT2 receptor inhibitors, hypoglycaemia would be expected to be less (13). Nauck (2011) 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 10mg once daily, since there appears to be little additional benefit from increasing the dose to 20mg. However we have, at present, only one study evaluating the 20mg 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

- The sulphonylureas
- Pioglitazone
- Acarbose
- The meglitinide analogues, nateglinide and repaglinide
- The GLP-1 analogues
- The DPP-4 inhibitors
- The 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 co-morbidities
- Ease of use, by oral administration rather than injection
- Cost

The fear of hypoglycaemia can have a significant impact on the patient's quality of life. 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 I diabetes.

Limitations of studies reviewed

There are no long-term data on SGLT2 side effects, both in terms of rare complications yet to be established, but also on the long-term effects of significant glycosuria on the urinary tract.

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 beta cell capacity.

Musso et al (2010) (14) produced an early systematic review into SGLT2 inhibitors that included 151 articles. The main reason for the difference in number of studies between our own review and that of Musso et al, is our focus is towards a very real world use of SLGT2 inhibitors. We excluded studies of less than 8 weeks in duration, whilst Musso et al analysed studies as short as 2 weeks. In addition, Musso et al included studies with SGLT2 inhibitors are primary intervention, whilst this study has only looked at SGLT2 inhibitors as in combination therapy.

Musso et al reach similar conclusions to our own, namely that SLGT2 inhibitors are effective at reducing HbA1c and fasting plasma glucose levels and BMI, whilst also observing a reduction in serum uric acid and blood pressure.

They come to similar conclusions about a ceiling of effectiveness for dapagliflozin doses of approximately 10-20mg/d

Musso et al conclude there is an increased risk of UTI with SGLT2 inhibitor, with an odds ratio of 1.34. In the present review, numbers of such infections were small in most studies. In the largest study, Nauck and colleagues reported more UTIs with dapagliflozin 2.5mg, 11% (95% CI 7.8 to 14.2%) versus 6% (3.6 to 8.4%) on placebo.

The US Food and Drug Administration (FDA) (15) reviewed dapagliflozin in July 2011. They felt unable to approve it without additional safety data, mainly because of concerns about bladder and breast cancer. In the studies 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 amongst 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 9 to 6 against approval.

Conclusion

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.

Competing interests of authors

None

Funding source – internal department

Contributions. Rachel Court carried out literature searches. All authors helped design the data extraction form. Christine Clar and James Gill extracted data. James Gill and Norman Waugh drafted the article which has been approved by all authors.

References

1. Diabetes UK,
Diabetes in the UK 2010: Key statistics on Diabetes
http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf
(Accessed October 1st 2011)

2. Mokdad AH, Ford ES, Bowman BA, Dietz W, Vinicor F, Bales V, Marks J.
Prevalence of Obesity, Diabetes, and Obesity-Related Health Risk Factors, 2001
A. JAMA. 2003; 289:76-79..1

3. Stone PH, Muller JE, Hartwell T.
The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis.
J. *Am Coll Cardiol.* 1989; 14:49–57

4. Santer R., Kinner M., Lassen CL., Schenppenheim R, Eggert P, Bald M, et al
Molecular Analysis of the SGLT2 Gene in Patients with Renal Glucosuria.
JASN 2003; 14: 2873-2882

5. Hanefeld M.
Dapagliflozin, an SGLT2 inhibitor, for diabetes.
Lancet 2010; 375:2196-2198

6. Higgins J. and Green S.
Cochrane Handbook for Systematic Reviews of Interventions (2008)
The Cochrane Collaboration. http://www.cochrane.org/training/cochrane-handbook
(Accessed Sept 1st 2011)

7. **Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications.**
Report of a WHO Consultation, WHO/NCD/NCS/99.2 (2000)
http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf
(Accessed Sept 20th 2011)

8. 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

9. Nauck MA, Del Prato S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al
Dapagliflozin Vs Glipizide as Add-on Therapy in Patients with Type 2 diabetes who have inadequate glycaemic control with Metformin
Diabetes care 2011; 34:2015-2022

10. Rosenstock J, Polidori D, Zhao Y, Sha S, Arbit D, Usiskin K et al.

Canagliflozin, an inhibitor of sodium glucose co-transporter 2, improves glycaemic control, lowers body weight, and improves beta cell function in subjects with type 2 diabetes on background metformin
Diabetologia 2010; 53:S349

11. 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 Obes. Metab. 2011; 13(10):928-938

12. 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

13. Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L, et al
Dapagliflozin a novel SGLT2 inhibitor induces dose-dependent glucosuria in healthy subjects.
Clin. Pharmacol Ther. 2009; 85:520-6

14. Musso G, Gambino R, Cassader M, Pagano G.
A novel approach to control hyperglycaemia in type 2 diabetes: Sodium glucose co-transport (SGLT) inhibitors. Systematic review and meta-analysis of randomised trials.
Annals of Medicine, 2011, Early On-line 1-19

15. Food and Drug Adminstration. Center for Drug Evaluation and Research
Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee
July 19, 2011

Appendix

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]				**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 Inhibitor Vs. metformin**
Aim: Determine if dapagliflozin, lowers HbA1c in type 2 diabetes in patients with inadequate HbA1c control with metformin				
Study Particulars	**Multi Centre:** 81 **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 RCT, double blind, placebo controlled **Primary outcome:** Change from baseline in HbA1c at week 24 **Secondary outcomes:** At 1 week, change in fasting plasma glucose At 24 weeks changes in: • Fasting plasma • Glucose concentration • No. with baseline HbA1c of 9% or more. • Proportion of patients achieving a therapeutic HbA1c, and • Total bodyweight.. • Change from baseline in bodyweight, and decreases in bodyweight of 5% or more.			
Participant Criteria	**N:** 534 analysed **Inclusion criteria:** participants aged between 18 years and 77; Type 2 diabetes, BMI <45kg/m2, HbA1c 7-10.0%; fasting C-peptide >0.34ng/ml, taking stable dose metformin>1500mg **Exclusion criteria (taken from paper):** (serum creatinine 133 µmol/L or more for men or 124 µmol/L or more for women (consistent with metformin labeling); urine albumin/creatinine ratio more than 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); and systolic blood pressure 180 mm Hg or more or diastolic blood pressure 110 mm Hg or more. Any significant other systemic disease **Lead in period:** 2 weeks, single blind, to assess compliance with placebo, patients randomised successful completion. Metformin dose stabilised to >1500mg			
Quality	**Study Quality:** medium – See Quality table for further information			
Participant baseline data	**Group 1 (n analysed=134):** Placebo OD + metformin,	**Group 2 (n= 135):** 2.5mg dapagliflozin OD, metformin	**Group 3 (n= 133):** 5mg dapagliflozin OD, metformin	**Group 4 (n= 132):** 10mg dapagliflozin OD, metformin
	Age: 53.7 SD 10.3 years **Sex:** 55% Male **BMI (KG/M^2):** 31.8 SD 5.3 **HbA1c (%):** 8.11% SD 0.96 **Duration of Diabetes:** 5.8 SD 5.1	**Age:** 55.0 SD 9.3 years **Sex:** 51% Male **BMI (KG/M^2):** 31.6 SD 4.8 **HbA1c (%):** 8.96% SD 2.39 **Duration of Diabetes:** 6.0 SD 6.2	**Age:** 54.3 SD 9.4 years **Sex:** 50% Male **BMI (KG/M^2):** 31.4 SD 5.0 **HbA1c (%):** 8.17% SD 1.0 **Duration of Diabetes:** 6.4 SD 5.8	**Age:** 52.7 SD 9.9 years **Sex:** 57% male **BMI (KG/M^2):** 31.2 SD 5.1 **HbA1c (%):** 7.92% SD 0.82 **Duration of Diabetes:** 6.1 SD 5.4

	FPG (mmol/l): 9.19 SD 2.57 **Systolic BP:** 127.7 SD 14.6		**FPG (mmol/l):** 8.96 SD 6.2 **Systolic BP:** 126.6 SD 14.5		**FPG (mmol/l):** 9.39 SD 2.7 **Systolic BP:** 126.9 SD 14.3		**FPG (mmol/l):** 8.66 SD 2.15 **Systolic BP:** 126.0 SD 15.9	
Outcome (change from baseline at study end)								
	Group 1 (n analysed=134): Placebo OD + metformin,		**Group 2 (n= 135):** 2.5mg dapagliflozin OD, metformin		**Group 3 (n= 133):** 5mg dapagliflozin OD, metformin		**Group 4 (n= 132):** 10mg dapagliflozin OD,	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ HbA1c (%)	-0.3	-0.44 to -0.16	-0.67	-0.81 to -0.53	-0.70	-0.85 to -0.56	-0.84	-0.98 to -0.70
Δ Weight (kg)	-0.9	-1.4 to -0.4	-2.2	-2.8 to -1.8	-3.0	-3.5 to -2.6	-2.90	-3.3 to -2.4
Δ FPG (mmol/L)	-0.33	-0.62 to -0.04	-0.99	-1.28 to -0.69	-1.19	-1.49 to -0.90	-1.3	-1.60 to -1.00
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Δ SBP (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	**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):** 2.5mg dapagliflozin OD, metformin		**Group 3 (n= 133):** 5mg dapagliflozin OD, metformin		**Group 4 (n= 132):** 10mg dapagliflozin OD,	
Specific Events	UTI: n= 11, GTI n = 7, HypoT n=1, HypoG n=4,		UTI: n= 6 GTI n = 11 HypoT n=0, HypoG n=3		UTI: n= 10, GTI n = 18 HypoT n=2, HypoG n=5,		UTI: n= 16, GTI n =12, HypoT n=0, HypoG n=5	
	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	
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits							

Nauck MA, Del Prato S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al **Dapagliflozin Vs Glipizide as Add-on Therapy in Patients with Type 2 diabetes who have inadequate glycaemic control with Metformin** Diabetes care 2011. 34:[2015-2022]		**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 Inhibitor + metformin vs metformin + glipizide**
Aim: Compare efficacy, safety and tolerability of dapagliflozin with glipizide, in patients with type 2 diabetes poorly controlled with monotherapy		
Study Particulars	**Multi Centre:** 95 sites across 10 countries World-wide **Duration of intervention**: 52 weeks **Duration of run in**: 2 weeks **Followup:** on completion of 52 weeks, a 156 week long-term study **Design:** 2-arm parallel group, RCT. **Primary outcome:** Absolute change from baseline in HbA1c at week 52 **Secondary outcomes:** - Change in total body weight - Proportion with hypoglycaemic episode - Proportion if ≥ 5% total weight loss.	
Participant Criteria	**N:** 801 analysed **Inclusion criteria:** participants aged 18 years and older; inadequately controlled type 2 diabetes, BMI ≤45kg/m2, HbA1c >6.5 and ≤10%; fasting C-peptide ≥0.33nmol/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, fasting plasma glucose ≤15mmol/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 x upper limit of normal; total bilirubin >34 µmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSH; systolic blood pressure ≥180mmHg and/or diastolic blood pressure ≥110 mmHg; significant other disease.	
Interventions	**Intervention 1:** 2.5mg dapagliflozin + metformin **Intervention 2:** 5mg glipizide + metformin **Lead in period:** 2 weeks, single blind placebo lead in prior to randomization. **All groups:** Patients randomly assigned to double blind therapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All patients maintained metformin	
Quality	**Study Quality:** medium – See Quality table for further information	
Participant baseline data	**Group 1** (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin	**Group 2 (**start n= 408, analysed n= 401): 5mg glipizide + metformin
	Age: 58 SD 9 years **Sex:** 55.3% Male **BMI (KG/M^2):** 31.7 SD 5.1 **≥ 25 kg/m^2**: 95%% **≥ 30 kg/m^2:** 57% **HbA1c (%):** 7.7% SD 0.9 **Duration of Diabetes:** 6 SD 5	**Age:** 59 SD 10 years **Sex:** 54.9§% Male **BMI (KG/M^2):** 31.2 SD 5.1 **≥ 25 kg/m^2**: 90.7% **≥ 30 kg/m^2:** 55.4% **HbA1c (%):** 7.7% SD 0.9 **Duration of Diabetes:** 7 SD 6

	FPG (mmol/l): 9.0 SD 2.1		**FPG (mmol/l):** 9.1 SD 2.3	
Outcome (change from baseline at study end)				
	Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin		**Group 2 (**start n= 408, analysed n= 401): 5mg glipizide + metformin	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ HbA1c (%)	-0.52	-0.60 to -0.44	-0.52	-0.60 to -0.44
Δ Weight (kg)	-3.22	-3.56 to -2.87	+1.44	+1.44
Δ FPG (mmol/L)	-1.24	-1.42 to -1.07	-1.04	-1.22 to -0.98
	Mean	**SD**	**Mean**	**SD**
Δ SBP (mmHg)	-4.3	-	-+0.8	-
HbA1c	-	-	-	-
Adverse Events	**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 ≥3%** 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 =*** *n=318* ***Group 2 =*** *n=318* No deaths in Dapagliflozin group 3 deaths in Glipizide group
	Group 1		**Group 2**	
Specific Events	UTI: n=44, GTI n = 50, HypoM n= 0 HypoS n= 7 HypoO, n=7 Events Leading to Discontinuation, n=0		UTI: n=26, GTI n = 11, HypoM n= 3 HypoS n= 147 HypoO, n=40 Events Leading to Discontinuation, n=6	
	Diarrhoea n= 19 Nausea n= 14 Vulvovaginal mycotic infection n= 14 Back pain n= 19 Nasopharyngitis n= 43 Cough n= 15 Influenza n= 30 Pain in extremity 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 Pain in extremity n= 21 Upper resp. Tract Infection n= 17 Headache n= 17 Hypertension n= 35	
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits			

Rosenstock J, Polidori D, Zhao Y, Sha S, Arbit D, Usiskin K et al. **Canagliflozin, an inhibitor of sodium glucose co-transporter 2, improves glycaemic control, lowers body weight, and improves beta cell function in subjects with type 2 diabetes on background metformin** Diabetologia 2010 53:[S349]	**Funding source:** *Johnson and Johnson* **Placebo + metformin** **Vs** **SGLT2 Inhibitor + metformin OD** **Vs** **SGLT2 inhibitor BD + metformin OD** **Vs** **sitaglipitin OD + metformin**
Aim: Assess the safety, tolerability and efficacy of an alternative SGLT2 inhibitor Canagliflozin and remaining beta cell function, in DM type 2 patients who have inadequate glycaemic control using metformin as a monotherapy.	
Study Particulars	**Multi Centre:** no comment in abstract **Duration of intervention**: 12 weeks **Duration of run in**: no comment in abstract **Follow-up:** no comment in abstract **Design:** 7-arm parallel group, RCT. Double blind, placebo controlled trial looking at metformin, canagliflozin 50, 100, 200, 300mg OD and 300mg BD, and sitaglipitin 100mg **Primary outcome:** Change from baseline in HbA1c and fasting plasma glucose at week 12 **Secondary outcomes:** Assess loss of beta cell function measured using HOMA2-B% derived from plasma glucose and C peptide
Participant Criteria	**N:** 451 analyzed against primary outcome **Inclusion criteria:** People with type 2 diabetes with inadequate glycaemic control using metformin monotherapy **Exclusion criteria (taken from paper):** no comment in abstract **Lead in period:** no comment in abstract
Quality	**Study Quality:** Medium – See Quality table for further information
	7 study groups, each group contained 64-65 patients, individual group numbers not given in abstract Baselines across all groups only given as overall average
Participant baseline data	**Age:** 53 **Sex:** - **BMI (KG/M^2):** 31.5 **HA1c (%):** 7.7% **Duration of Diabetes:** - **FPG (mmol/l):** 9.0 **Systolic BP:** -

Outcome (change from baseline at study end)								
	Group 1 placebo + metformin		**Group 2** canagliflozin 50mg + Metformin		**Group 3** canagliflozin 100mg + metformin		**Group 4** canagliflozin 200mg + metformin	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ HbA1c (%)	-0.2	-	-0.45	-	-0.51	-	-0.54	-
Δ Weight (kg)	-	-	-1.3	-	-1.5	-	-1.6	-
Δ FPG (mmol/L)	-	-	-0.9	-	-1.4	-	-1.8	-
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Δ SBP (mmHg)	-	-	-	-	-	-	-	-
HbA1c	7.5	0.96	7.2	0.88	7.1	0.85	6.9	0.68
	Group 5 canagliflozin 300mg + metformin		**Group 6** canagliflozin 300mg BD + metformin		**Group 7** sitagliptin + metformin			
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**		
Δ HbA1c (%)	-0.71	-	-0.73	-	-0.56	-		
Δ Weight (kg)	-2.3	-	-2.3	-	+0.4	-		
Δ FPG (mmol/L)	-1.8	-	-1.7	-	-1.0	-		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Δ SBP (mmHg)	-	-	-	-	-	-		
HbA1c	6.8	0.82	6.8	0.72	6.9	0.92		
Adverse Events	***At least one or more adverse event balanced across all arms save for:***							
Specific Events	***Genital tract infections:*** *3-8% canagliflozin arms* *2% placebo* *2% sitagliptin*		***UTI*** *3-9% canagliflozin arms* *6% placebo* *2% sitagliptin*		***Hypoglycaemia*** *(not defined in abstract)* *0-6% canagliflozin arms* *2% placebo* *5% sitagliptin*			
	All AE were seen to be non-dose dependent **After 12 weeks no "safety signals" (not defined in abstract) in lab studies, ECG or vital signs were seen in Canagliflozin arms** **Similar incidences of discontinuation due to adverse events, although number not specified** **Number of severe adverse events not given**							
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits							

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 Obes. Metab. 2011 13(10):[928-938]				**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **2.5, 5, 10mg SGLT2 Inhibitor (dapagliflozin) vs 4mg glimepiride**
Aim: To determine 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				
Study Particulars	**Multi Centre:** 84 sites across 7 countries **Duration of intervention**: 52 weeks **Duration of run in**: 2 weeks **Follow-up:** on completion of 52 weeks, a 156 week long-term study **Design:** 2-arm parallel group, double-blind RCT **Primary outcome:** Absolute HbA1c change from baseline to week 24 **Secondary outcomes:** - Total body weight after 24 weeks - Change from baseline after week 24 in post challenge plasma glucose (2hrs) following oral glucose tolerance - Proportion of patients with HBA1c <7% after 24 weeks - Total body weight from baseline if BMI ≥27kg/m^2 • FPG from baseline after 24weeks			
Participant Criteria	**N:** 592 analyzed **Inclusion criteria:** Participants aged 18 years and older; inadequately controlled type 2 diabetes, BMI ≤45kg/m^2, HbA1c of ≥7 to ≤10.0%; 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, fasting plasma glucose ≤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 x upper limit of normal; total bilirubin >34 µmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSH; SBP ≥180 mmHg and/or DBP ≥110 mmHg. Any significant other systemic disease			
Interventions	**Intervention 1:** placebo plus 4 mg/day glimepiride **Intervention 2:** 2.5 mg/day dapagliflozin plus 4 mg/day glimepiride **Intervention 3:** 5 mg/day dapagliflozin plus 4 mg/day glimepiride **Intervention 4:** 10 mg/day dapagliflozin plus 4 mg/day glimepiride **Lead in period:** 1 week for inclusion/exclusion review for those switched to 4 mg/day glimepiride **All groups:** dapagliflozin double-blind, glimepiride open label; glimepiride allowed to be down-titrated to 2 mg/day or discontinued in case of hypoglycaemia, no up-titration allowed; in case of inadequate glycaemic control, patients could receive open-label rescue therapy of metformin, pioglitazone or rosiglitazone; all patients received dietary and lifestyle counseling and patients with BMI ≥27 kg/m^2 received advice regarding reducing caloric intake and increasing physical activity			
Quality	**Study Quality:** Medium – See Quality table for further information			
Participant	**Group 1 (n= 146)**	**Group 2 (n= 154)**	**Group 3 (n= 145)**	**Group 4 (n= 151)**

baseline data	Placebo + glimepiride		2.5mg dapagliflozin + glimepiride		5mg dapagliflozin + glimepiride		10mg dapagliflozin + glimepiride	
	Age (years): 60.3 SD 10.16 **Sex:** 49% male **BMI (kg/m^2)** **≥ 25 kg/m^2**: 86.2% **≥ 30 kg/m^2:** 45.5% **HbA1c (%):** 8.15 SD 0.74 **Duration of diabetes (years):** 7.4SD 5.7 **FPG (mmol/L):** 9.58 SD 2.07 **Systolic BP (mmHg):** 133.3		**Age (years):** 59.9.3 SD 10.14 **Sex:** 50% male **BMI (kg/m^2)** **≥ 25 kg/m^2**: 84.4% **≥ 30 kg/m^2:** 48% **HbA1c (%):** 8.11, SD 0.75 **Duration of diabetes (years):** 7.7 SD 6.0 **FPG (mmol/L):** 9.56, SD 2.13 **Systolic BP (mmHg):** 134.6		**Age (years):** 60.2 SD 9.73 **Sex:** 50% male **BMI (kg/m^2)** **≥ 25 kg/m^2**: 78% **≥ 30 kg/m^2:** 50% **HbA1c (%):** 8.12 SD 0.78 **Duration of diabetes (years):** 7.4 SD 5.7 **FPG (mmol/L):** 9.68 SD 2.12 **Systolic BP (mmHg):** 130.9		**Age (years):** 58.9 SD 8.32 **Sex:** 43.7% male **BMI (kg/m^2)** **≥ 25 kg/m^2**: 79.4% **≥ 30 kg/m^2:** 45.% **HbA1c (%):** 8.07 SD 0.79 **Duration of diabetes (years):** 7.2 SD 5.5 **FPG (mmol/L):** 9.55 SD 2.04 **Systolic BP (mmHg):** 133.8 SD 15	
Outcome (change from baseline at study end)								
	Group 1 (n= 146) Placebo + glimepiride		**Group 2 (n= 154)** 2.5mg dapagliflozin + glimepiride		**Group 3 (n= 145)** 5mg dapagliflozin + glimepiride		**Group 4 (n= 151)** 10mg dapagliflozin + glimepiride	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ from baseline HbA1c (%)	-0.13	-	-0.58	-0.61 to -0.27	-0.63	-0.67 to -0.32	-0.82	-0.86 to -0.51
Δ from baseline Weight (kg)	-0.72	-	-1.18	-1.08 to +0.15	-1.56	-1.47 to -0.21	-2.26	-2.17 to -0.92
Δ from baseline FPG (mmol/L)	-0.33	-	-2.08	-2.50 to -1.00	-1.78	-2.20 to -0.68	-1.94	-2.34 to 0.87
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Absolute Δ SBP from placebo (mmHg)	-1.20	-	-4.7	-6.1 to -0.9	-4.0	-5.5 to -0.2	-3.8	-6.4 to -1.2
HbA1c	-	-	-	-	-	-	-	-
Adverse Events	**General events – where frequency is ≥3% in any group** UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia				Hypoglycaemia defined as blood sugar <70mg/dl)		***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 2.5mg 1 death in Dapagliflozin 10mg	
	Group 1 (n= 146)		**Group 2 (n= 154)**		**Group 3 (n= 145)**		**Group 4 (n= 151)**	

	Placebo + glimepiride	2.5mg dapagliflozin + glimepiride	5mg dapagliflozin + glimepiride	10mg dapagliflozin + glimepiride
Specific Events	UTI: n=9, GTI n = 1, ≥ 1Hypo n= 7	UTI: n=6, GTI n = 6, ≥ 1Hypo n= 11	UTI: n=10, GTI n = 9, ≥ 1Hypo n= 11	UTI: n=8, GTI n = 10, ≥ 1Hypo n= 12
	Bronchitis n= 4 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	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= 4 Hypertension n= 2
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits			

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]	**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 Inhibitor + patients own oral antidiabetic drugs (OAD) Vs insulin + OAD**
Aim: Determine if Dapagliflozin, lowers HBA1c in Type 2 diabetes in patients with type 2 diabetes poorly controlled with high insulin doses plus oral antidiabetic agents	
Study Particulars	**Multi Centre:** 26 sites (USA and Canada) **Duration of intervention**: 52 weeks **Duration of run in**: 2 weeks **Follow-up:** on completion of 52 weeks, a 156 week long-term study **Design:** 2-arm parallel group, RCT **Primary outcome:** Change from baseline in HbA1c at week 12 **Secondary outcomes:** - Change from baseline FPG - Change in total daily requirement of insulin - Percentage of patients with change in HbA1c >0.5% - Percentage of end patients with final HbA1c <7%
Participant Criteria	**N:** 65 analysed **Inclusion criteria:** Participants aged between 18 years and 75; type 2 diabetes, BMI ≤45 kg/m^2, HbA1c of 7.5-10.0%; taking stable dose metformin (≥1000mg) and/or pioglitazone (≥30mg) for ≥6 weeks and insulin therapy (50 units) ≥12 weeks before enrolment. Fasting C-peptide ≥0.8 ng/ml, serum creatinine <1.5 mg/dl (men) or <1.4 mg/dl (women), and a 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 limits of normal, creatine kinase ≥3 times the upper limits of normal, symptoms of severely uncontrolled diabetes including a history of severe hypoglycemia. Any significant other disease
Interventions	**Intervention 1:** placebo plus stable dose of insulin sensitizer (metformin and/or pioglitazone) plus insulin (50% of pre-study dose)

	Intervention 2: 10 mg dapagliflozin once daily plus insulin sensitizer and insulin as in intervention 1 **Intervention 3:** 20 mg dapagliflozin once daily plus insulin sensitizer and insulin as in intervention 1 **All groups:** insulin dose reduced to 50%; diet and exercise programme (American Diabetes Association or similar local guidelines); following lead in period there were no dose adjustments to OADs; insulin could be down-titrated in patients at risk of hypoglycaemia **Lead in period:** 10-21 day to establish reduced insulin dose					
Quality	**Study Quality:** Medium – See Quality table for further information					
Participant baseline data	**Group 1 (n analysed=19):** Placebo, OADs + insulin,		**Group 2 (n= 23):** 10mg dapagliflozin, OADs + insulin,		**Group 3 (n= 23):** 20mg dapagliflozin OD, OADs + insulin,	
	Age (years): 58.4 SD 6.5 **Sex:** 69.6% male **BMI (kg/m^2):** 34.8 SD 4.6 **HbA1c (%):** 8.40% SD 0.9 **Duration of diabetes (years):** 7.4SD 5.7 **FPG (mmol/L):** 9.22 SD 2.86 **Systolic BP (mmHg): n/a**		**Age (years):** 55.7 SD 9.2 **Sex:** 54.2% male **BMI (kg/m^2):** 35.5 SD 3.6 **HbA1c (%):** 8.4% SD 0.7 **Duration of diabetes (years):** 11.8 SD 5.8 **FPG (mmol/L):** 8.67 SD 2.17 **Systolic BP (mmHg): n/a**		**Age (years):** 56.1 SD 10.6 **Sex:** 54.2% male **BMI (kg/m^2):** 36.2 SD 4.6 **HbA1c (%):**8.5% SD 0.9 **Duration of diabetes (years):** 11.3 SD 5.6 **FPG (mmol/L):** 8.98 SD 3.06 **Systolic BP (mmHg): n/a**	
Outcome (change from baseline at study end)						
	Group 1 (n analysed=19): Placebo, OADs + insulin,		**Group 2 (n= 23):** 10mg dapagliflozin, OADs + insulin,		**Group 3 (n= 23):** 20mg dapagliflozin OD, OADs + insulin,	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ HbA1c (%)	+0.09	-0.2 to +0.4	-0.61	-0.9 to -0.4	-0.69	-0.90 to -0.4
Δ Weight (kg)	-1.9	-2.9 to -0.9	-4.50	-5.5 to -3.5	-4.3	-5.3 to -3.3
Δ FPG (mmol/L)	+0.99	+0.08 to +1.90	-0.13	-0.75 to +1.02	-0.53	-1.42 to +0.35
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Δ SBP (mmHg)	-	-	-7.2	-	-6.10	-
HbA1c	8.5	0.8	7.80	0.7	7.80	0.60
Adverse Events	**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=15* ***Group 2** = n=18* ***Group 3** = n=16* *One patient in each group discontinued due to adverse effects*	
Specific Events	**Group 1 (n analysed=19):** Placebo, OADs + insulin,		**Group 2 (n= 23):** 10mg dapagliflozin, OADs + insulin,		**Group 3 (n= 23):** 20mg dapagliflozin OD, OADs + insulin,	
	UTI: n=0, GTI n = 1, HypoT n=n/a, HypoG n=3		UTI: n= 0, GTI n = 0, HypoT n=n/a, HypoG n=7,		UTI: n= 1, GTI n = 5, HypoT n=n/a, HypoG n=6	
	Nausea n= 1 Pollakiuria n= 4 Back pain n= 2 Nasopharyngitis n= 2 Abdominal pain n= 2		Nausea n= 1 Pollakiuria n= 2 Back pain n= 3 Nasopharyngitis n= 2 Fatigue n= 2		Nausea n= 3 pollakiuria n= 3 vomiting n=3 Vulvovaginal mycotic infection n=3 Anxiety n=2	

	Influenza n= 2 Pain in extremity n= 1 Upper resp. Tract Infection n= 2 Headache n= 2 Procedural pain n=2	Influenza n= 1 Pain in extremity n= 2 Upper resp. Tract Infection n= 2 Headache n= 3 Pharyngolaryngeal pain n=2	Back pain n= 2 Dry Mouth n=2 Nasopharyngitis n=2 Peripheral odema n=2 Abdominal pain n=2 Fatigue n= 1 Influenza n= 1 Pain in extremity n= 1 Upper resp. Tract Infection n= 1
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits		

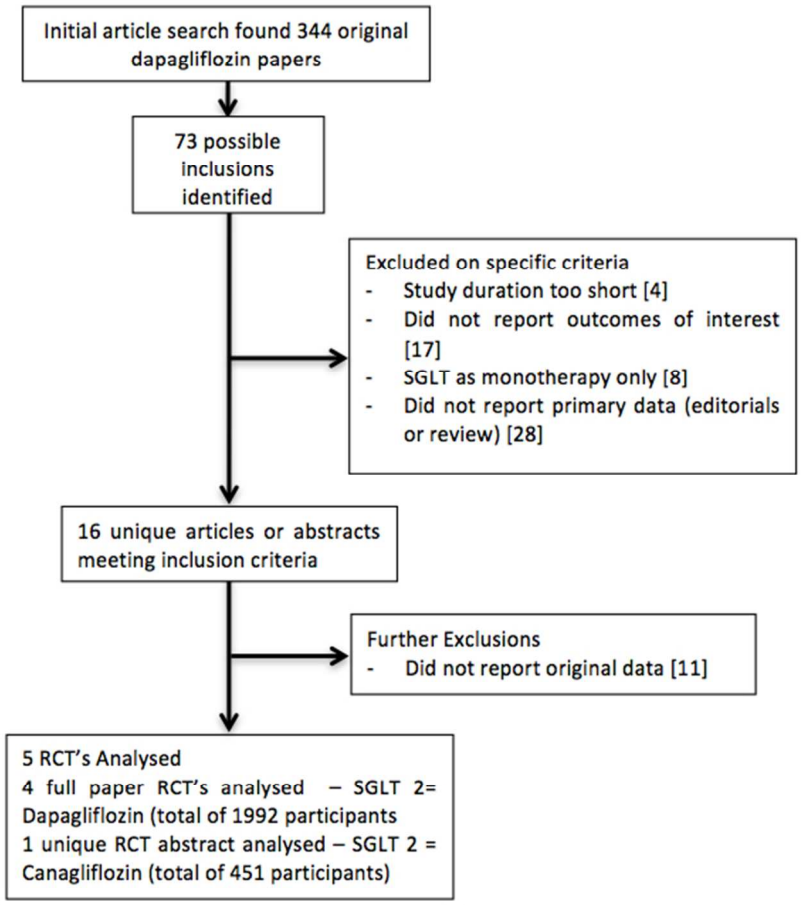


Image of figure 1

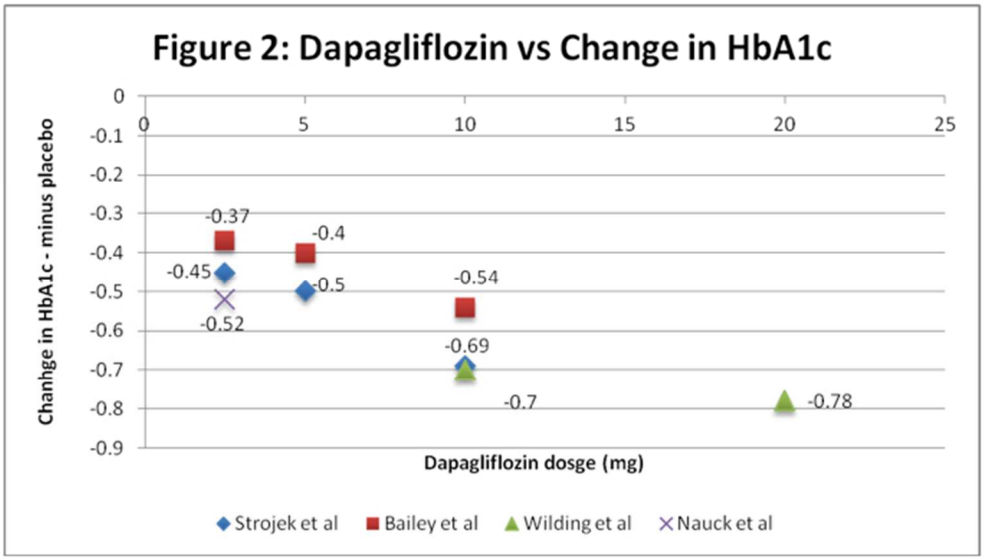


image of figure 2

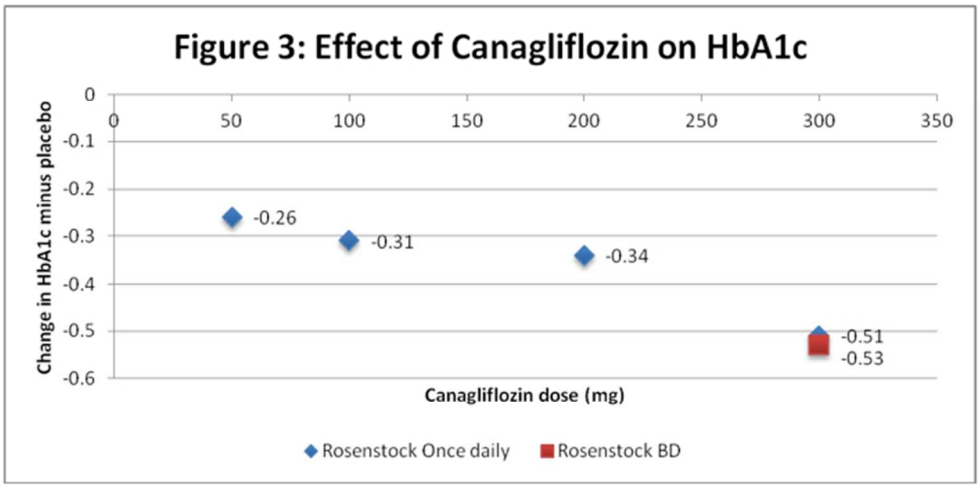


image of figure 3

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Systematic Review of SGLT2 Receptor Inhibitors in dual or triple therapy in type 2 diabetes

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Complete List of Authors:	Waugh, Norman; Warwick University, Division of Health Sciences Clar, Christine Gill, James; University of Wariwick, Division of Health Sciences; University Hospitals Coventry and Warwickshire, Endocrinology Court, Rachel; Warwick University, Division of Health Sciences
Primary Subject Heading:	Diabetes and endocrinology
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PRISMA 2009 Checklist Gill et al 2012

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	no
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3 to 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	tables
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7

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Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	tables
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	tables
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Dapifloz peer review responses

Reviewer 1	
Written english is okay bit they did a ton of bullets that should be changed. Again, mentioned this in comments to authors.	
Major comments	
Overall comments: This is a systematic review discussing the SGTL2 receptor inhibitors used as combination therapy for treatment of type 2 diabetes. While this is an important topic as we need to know what is the best 2nd and 3rd line agent for type 2 diabetes, the article is limited in the lack of trials to include in this systematic review which make it tough to draw many conclusions regarding safety outcomes. In addition, only one of the studies is an active comparator while the rest are placebo controlled trials making the data less useful since we can't determine the comparisons between adding januvia versus an SGLT2 inhibitor for instance based on the data available. However, it does provide information on the general efficacy of SGLT2 inhibitors when used as combination therapy.	Fair points, but we can only report what research there is. And it is not correct that only one trial had an active comparator – there were two active comparators, glipizide in Nauck 2011 and sitagliptin in Rosenstock 2010.
1) The introduction needs to address why this topic needed a systematic review. i.e. Few people know about the potential benefits or harms of SGTL2 inhibitors used as dual or triple combination therapy for type 2 diabetes; therefore, we decided to conduct as systematic review of SGTL2 inhibitors to assess the efficacy and safety of these agents used as combination therapy for adults with type 2 diabetes. Would add safety not just efficacy into all statements where you say you are assessing efficacy since you do also	Section added at end of Introduction with similar message to referee's comments, and mentioning safety.

assess safety in your results.	
2) The appendix table is okay but is so big and long that it does not provide a great summary of the articles within one viewing segment. I would recommend another summary table showing key aspects of the study so that all 5 articles can be viewed on one page listing in columns: N of participants, dose of drug in each arm and names of drugs in each arm can be listed as rows under each study, mean baseline a1c, mean age, gender, key inclusion/exclusion criteria, country of study, study quality, and change in a1c between groups (which can be calculated) and whether statistically significant differences between groups or not.	A summary table with all the variables suggested by the referee would be rather large, but we take the point that a summary table would be useful. We have inserted one which is not quite as extensive as he suggested.
3) The discussion talks about the lack of long term data on safety and long term outcomes but does not mention the potential safety concerns of cancer, liver toxicity, and nephropathy. These were brought up in the FDA review of the drug and was why it was not yet FDA approved. I think it is reasonable to mention these issues to the reader and note that we need further studies specifically in these areas to address potential concerns of specific adverse effects.	We have added a paragraph on the FDA review.
4) I found the article results difficult to follow since there was no range in mean differences between groups. This could probably be helped by either putting that in the text or adding the summary table to the article as discussed in #2.	Table added
Minor issues	
1) Abstract background: consider adding at the end of the sentence “, and little is known regarding their efficacy and safety when used as dual or triple therapy for type 2 diabetes.” This will help make it	We have added some text to the Objective in the Abstract to make it clear that our review is about the use of these drugs in dual or triple therapy.

more clear to the reader why a systematic review needs to be conducted.	
2) Abstract objective: consider adding "and safety" after effectiveness. May want to change effectiveness to efficacy since data are all from RCTs which are mainly efficacy trials not effectiveness trials done in the "real world".	Safety added.
3) Abstract Inclusion criteria: consider adding randomized before the word trials.	We have added "randomised controlled"
4) Abstract Results: Seems like you could put the range in between group differences for a1c and weight loss for the placebo controlled trials here. Also, trial quality appeared good does not sound scientific. You used a validated instrument to assess risk of bias-why not provide the quantitative results of that assessment in results.	Figures for HbA1c changes added to Abstract. No change to "good quality" – it's a standard expression in systematic reviews. Text on safety added to Abstract.
5) Globally, I have never seen an article use so much bulleting before. One problem with bulleting is you feel a bit like you are reading an outline in some parts as opposed to a written article. Please fix that throughout unless the editor states differently. I would write it as a sentence with commas wherever this occurred.	We don't think the use of bullets is excessive but will amend it if the editor wishes.
6) I also found it hard to follow the headers since I am so used to articles being laid out in specific ways. (i.e. background, methods, results, and discussion). Usually, I only see subheadings under methods and results. I thought the subheadings in the background should be removed (i.e. subheading decision problem and review objectives – can keep text under subheadings just do not need the subheadings in my opinion – I found it	We have amended the structure slightly by having bolder headings for Introduction, Methods, Results, Discussion. We have removed the subheading on objectives, and the sentence that followed it, from the Introduction, and have expanded the preceding paragraph. However we have kept the subheadings in Methods and Results.

confusing), and under methods need to make less subheadings - could divide into 3 sections: data sources and selection (include search strategy, inclusion/exclusion criteria here), data extraction and quality assessment, and data synthesis and analysis.	
7) Would add rationale for systematic review as mentioned under major issues above prior to subheading listed as review objectives.	Done
8) Would consider removing the sentence under decision problem that states we start from the position that the first line drug in type 2 diabetes is metfromin… Although I agree that these meds are unlikely to replace metformin, you do not need the sentence since will state rationale for why you are looking at it in combination therapy. You could add a sentence earlier instead when talking about rationale for not looking at it in monotherapy by stating that a recent systematic review has already evaluated the class as monotherapy.	Paragraph removed – having expanded what is now the last paragraph of the Introduction, we no longer need the "Decision problem" section. Sentence added.
9) Above participants on page 3, delete the two sentences above participants which discuss outcomes and looking at trials against placebo since this should be and is under methods already. Redundent and does not need to be here.	We have removed the sentence on outcomes, since those appear in the Methods section. However since Questions 1 and 2 focus on active comparators, we think it is worth retaining the sentence on placebo trials. We have reduced the length of this section by amalgamating questions 1 and 2.
10) Would start methods before study participants and all the following information should be put without bullets under one of the three headings mentioned above.	Methods now starts as suggested. Subheadings retained
11) Would remove all times when you state "if data permitted". You are just describing methods here. In results, you can state that there were no data to answer a specific question.	Done

12) In methods when you describe looking at subgroups, would consider removing the categories of duration. Not needed really. Just use the statement that you already have regarding exploring duration of diabetes.	Categories retained because this was to address a specific hypothesis
13) Report methods for synthesis of evidence of clinical effectiveness. I would move this sentence to right above your discussion of data synthesis and add the words "to be described in detail below".	OK, done, and subheading removed.
14) Study selection: would add the words inclusion/exclusion before the word criteria for clarity.	OK, done
15) I could not tell if the quality assessment was done independently by 2 reviewers. The word verified should be changed if it was done independently as verified makes me think someone only looked over someone's else's answers in which case it would be a serial not an independent review.	Changed from "independently verified" to "checked".
16) Usually the Figure 1 has two boxes above the one listed there. One box shows all sources of data and N of titles reviewed (i.e. medline N=12000, handsearch N=29, embase N=13000 with an N excluded between title and abstract review. A second box listing N abstracts reviews would come above N full articles reviewed with an arrow to the side listing N of exclusions. Usually there are some reasons for exclusion listed between abstract and full article review boxes – would add that here if available. Would also remove fig 1 from box and have as a title. "Figure 1: Study flow diagram" or Figure 1: literature search results could be used for instance.	The sources of data are in the text. Title of figure amended and text below moved to start of Results.
17) Would move results header to above the	Results heading moved, but most subheadings

sentence on literature search results. Would remove subheaders of participants, interventions, leadin periods, and power. Would consider replacing with one heading called study characteristics and quality or could have study characteristics followed by quality then rest of headers as is. Power paragraph should go under a more global assessment of quality. You provide the quality table but only discuss power in the text. Would choose a few key issues such as allocation concealment and total dropout from the table to discuss in the text as one quality paragraph total.	retained.
18) Would change figure 2 header to change in a1c by dapagliflozin dose.	Done
19) If able, would be useful to have standard error bars in figures 2 through 5	Some figures removed
20) Under SBP, mention if compared to placebo here so it is obvious to the reader. Would make sure that is clear for all results.	Fair point. Text added to clarify.
21) It was not clear from the article that dapagliflozin reduces SBP based on 2 articles. In discussion, could say that it may also reduce SBP but need more data to further substantiate this or please make more evident why you think this is true. I did not feel that two RCTs with small differences in one of them was sufficient to say with certainty and unclear from results if the -2.7 was statistically significant.	All four dapagliflozin trials reported SBP reductions.
22) In discussion, you list SGLT2 inhibitors under nine classes. Are these available for use in Canada? If so, keep here. If not, may want to point out that the other 8 classes are available for use and that this class is not yet approved for use in all	Being based in the UK, we don't know what is available in Canada. All the other 8 classes are available in the UK, and dapagliflozin is expected to be submitted for licensing soon.

countries.	
23) Limitations – you state wilder noted one case of renail failure. Seems like that should also be listed under adverse events section under results.	Ok, moved to Adverse events section
24) Statement about wilder matching by demographics but could be biased by differences in prior med use seemed a bit strange. If this was an RCT, then shouldn't the background meds have been similar between groups? Was it not?	Fair point. Sentence deleted.
25) Usually I see ceiling of effectiveness written as ceiling effect but that is in the US. If the Canadian terms are different, then leave as is. If not, then would change to ceiling effect.	No change. There could be ceiling effects in adverse events too
26) In discussion, you state that UTIs were only mild infections not requiring treatment. May be worth adding a statement afterward that we need more studies with more people to have sufficient power to determine if there were differences in more serious UTIs requiring treatment.	OK, text revised and we have added the figures from Nauck, the largest study and calculated percentages and CIs.
27) In conclusions, you state that SGLT2 inhibitors appear safe as much as can be assessed via short term trials. I would probably take the safe part out here – you could comment on the hypoglycemia effect if you want. You could state that they are effective at reducing a1c and weight. I would add a sentence stating that we can not be sure of its impact on long term outcomes or safety until long term large studies are conducted assessing both long term outcomes and rare adverse events such as cancer, renal failure, and liver toxicity among others.	Safe bit removed and paragraph on FDA review added.
28) Abstract conclusion – would remove safe	Done.

from the sentence and would state effective at reducing a1c and weight in short term RCTs.	
Reviewer 2 Jennifer Hirst	
Presentation of results in the abstract is too brief and and needs to provide an answer to the research questions	Abstract is already close to word limit.
Text in search methods states that 344 hits were returned from searches whereas Figure 1, the Flow chart only begins with 73 articles. Nowhere in the text is this discrepancy clarified.	Figure 1 revised to clarify this
A description of the statistical methods needs to be given.	None used.
On page 6 details of study participants are presented, with numbers in brackets, it needs to be made clear whether these numbers represent the range or confidence intervals.	Clarified by addition of “range”
References for all the included studies should be included in the reference list.	Done
Written presentation: Page 6 - Lead in periods - wording in the last sentence is unclear: "Only in the Rosenstock..."	Revised
Page 8 Body Weight - the first sentence extends to 6 lines and needs breaking into at least 3 sentences.	Revised
Page 8 last sentence - not clear what the message is here.	That weight loss in trials may be due to being in the trial not due to the drugs.
Appendix. One of the studies in the table (Rosenstock) has no details of number of participants	The total number is given.
Appendix: pages 15 and 16 - Group 4 -10mg dapagliflozin - is this in combination with metformin? If not, then it does not meet the	Yes is in combination with metformin – added to box.

inclusion criteria.	
The results of this systematic review have been presented in graphical format, with data points from all included studies plotted together. In this format it is difficult to interpret the data, though the authors have attempted to do this through narrative and overall statements. The authors state that a meta-analysis was not conducted because of the small number and heterogeneity of the trials. As 5 trials have been included in the review, and each of these report outcomes which can be compared, a meta-analysis could be conducted. The authors throughout the paper make summary statements about the results, however the method of analysis used by the investigators is not appropriate to draw these conclusions. A meta-analysis should be conducted and would substantially improve the paper.	A meta-analysis would have been entirely inappropriate because of the heterogeneity of the studies. No – a meta-analysis should not be done. You can't combine a study of triple therapy with others of dual, or one of canaglifozin with some of dapagliflozin, or studies with different comparators.
A table summarising the study characteristics of included studies is needed in the results section. Suggest to include details of intervention & comparator medications, numbers of participants in each arm, dose and length of study.	Table added with the arms of most interest.
The curved line connecting the points on the graphs implies that the trend has been observed. As this is not the case, a straight line or preferably a dotted line would be more appropriate. In addition, confidence intervals should be provided on the graphs, with data points being slightly offset so confidence intervals can be seen.	Lines removed.
Results - 1st paragraph - in the text report SGLT2 inhibitors to lower HbA1c by between -0.52 and -0.78%, but Figure 2 shows this to be	Corrected.

between -0.37 and -0.78%	
-2nd paragraph - "no difference ... between dapagliflozin and glipizide" - Figure 2 appears to show a comparison of 2.5mg and 5mg. It is misleading to present data from an arm of the trial without dapagliflozin in this graph.	Accepted, and glipizide cross removed
There is no discussion of Figure 3 or Figure 5	Figure 3 now discussed. Figures 4 and 5 removed
Body weight - median weight reduction of -2.33kg presented with confidence intervals. Is this mean rather than median? How was this calculation perfomed and which statistical package was used to get to this value? This value should be obtained using meta-analysis.	Figures were as calculated in original studies. No meta-analysis should be done.
Significant reductions in weight, blood pressure and FPG reported without supporting statistics (means and confidence intervals).	
Hypoglycaemic - "a small but not significantly significant increase in ..... hypoglycaemia across 3 of the 4 studies" - The way the data is presented makes it difficult to judge whether hypoglycaemia is an issue. A meta-analysis of this data is needed to clarify this.	No change
Page 11 - 3rd paragraph. - "optimum dosage ...between 10-20mg" - of your 5 trials, there was only 1 trial which used a dose of over 10mg, and this was the smallest of the included trials with a maximum of 23 patients in each arm. No confidence intervals are presented, it is therefore not possible to say whether the observed difference at 20mg is significantly different from that at 10mg. There is insufficient evidence presented to conclude that an	Fair point, and paragraph replaced with new one.

optimum dosage of 10-20mg.	
The presentation of the results in this review needs to be revised. This could be achieved by conducting a meta-analysis. Data could then be presented in subgroups of dose. A summary statistic estimate need not be presented particularly if heterogeneity is large, but should be considered. The authors are strongly urged to conduct a meta-analysis of their data.	We remain convinced that a meta-analysis would not be appropriate.

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Title: 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: Five trials, published in full, assessed dapagliflozin and one assessed canagliflozin. Trial quality appeared good for the published trials. Dapagliflozin 10mg reduced HbA1c, after adjustment for placebo change, by 0.54% to 0.7 compared to placebo, but there was no difference compared to glipizide. Canagliflozin reduced HbA1c slightly more than sitagliptin (reductions of 0.71% and 0.56%). Both dapagliflozin and canagliflozin led to weight loss.
Limitations: trials were short term. No breakdown of relative effectiveness by duration was available. Data on canagliflozin is 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 FDA 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.

Introduction

Type 2 diabetes is one of the most important and prevalent chronic diseases today, with in 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 (NICE), recommend that if lifestyle intervention is insufficient, the first line of drug treatment is metformin, followed by a sulphonylurea, or sometimes a glitazone, before commencing 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 anti-diabetic medications need to not only 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 (160-180mg/dl) has been reached. At this threshold the proximal tubule cannot reabsorb all of the filtered glucose, resulting in glycosuria. 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 to 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, also 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 SGLT-2 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, e.g. metformin plus SGLT2 versus metformin plus sulphonylurea, and in triple therapy, e.g. metformin, sulphonylurea and SGLT2 inhibitor versus metformin, sulphonylurea and dipeptidyl peptidase 4 inhibitors (DPP4) such as sitagliptin

We also look at 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 Cochrane Handbook for Systematic Reviews of Intervention (6)

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 longer than 10 years

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

Interventions:

- Any use of SGLT2 inhibitors in dual or triple therapy, in addition to other interventions including, but not restricted to: sulphonylureas, insulin and gliptins.

Outcome measures.

The outcomes sought were:

- Glycaemic control as reflected in HbA1c – taken as the main outcome of interest
- Change in weight (Kg) or body mass index
- Adverse effects, including hypoglycaemia, UTI and change in quality of life
- Cardiovascular events

Study Design

Randomised control trials (RCT) and systematic reviews of trials are used for 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 to be detected in HbA1c levels due to turnover of red blood cells.

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

Search methods for identification of studies

We searched the following sources:

- MEDLINE
- MEDLINE in-Process
- EMBASE
- The Cochrane Library, all sections
- NHS HTA

- Science Citation Index Expanded (SCI expanded)
- On-going Trials Registers:
- Clinical trials (www.clinicaltrials.gov)
- Current Control Trials (www.controlled-**trials**.com/)
- American Diabetes Association – Conference Abstracts
- EASD – 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. Initially returning 344 hits after the removal of duplications. 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. SGLT-2 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.

Data collection and analysis

Study Selection: two reviewers using the defined inclusion and exclusions criteria above selected studies independently. 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.

The quality of the individual studies was assessed by one reviewer using the Cochrane Risk of Bias score (6) and checked by a second reviewer. Any disagreements were resolved by discussion.

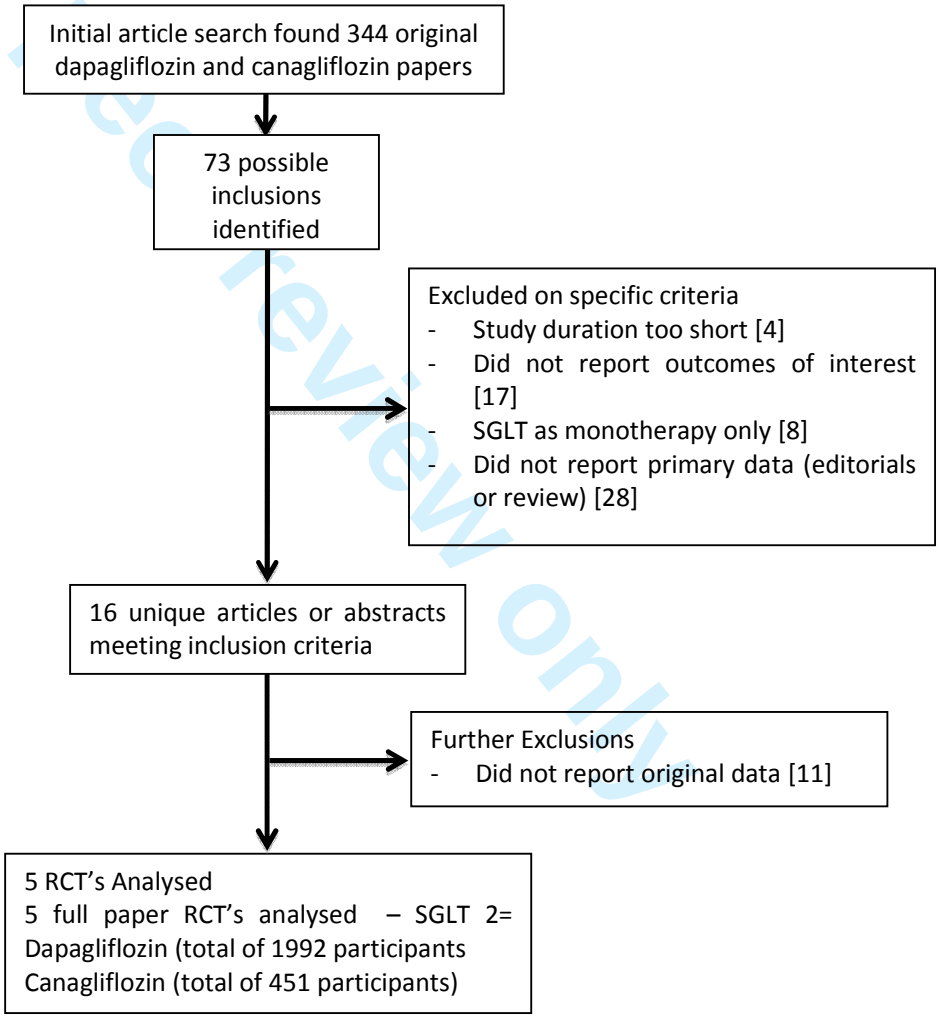
Data synthesis and analysis

This data analysis has been reported according to the guide set down within the Cochrane Handbook for Systematic Reviews of Interventions (6). No meta-analysis was possible due to the small number and heterogeneity of trials.

Results

The results of the literature search are shown in figure 1. After exclusions, made according to the study protocol, 5 RCTs published in full, covering 20 different comparisons remained for analysis.

Figure 1: search results



$These studies are summarised in table 1

Table 1: Summary of trials (selected arms only) and change in HbA1c.

Study	SGLT2 inhibitor	Comparator	Baseline HbA1c	Change in HbA1c	Difference
Bailey 2010 (8)	dapaglifozin 10mg + metformin	Placebo + metformin	dap 7.9% pbo 8.0%	- 0.84% - 0.3%	0.54%
Nauck 2011 (9)	dapagliflozin 2.5mg + metformin	glipizide 5mg + metformin	dap 7.7% glip 7.7%	- 0.52% - 0.52%	No difference
Rosenstock 2010 (10)	canagliflozin 300mg once daily	sitagliptin	can 7.7% sita 7.7%	- 0.71% - 0.56%	0.15%
Strojek 2011 (11)	dapaglifozin 10mg + glimepiride 4mg	glimepiride 4mg + placebo	dap 8.07% pbo 8.15%	- 0.82% - 0.13%	0.69%
Wilding 2009 (12)	dapaglifozin 10mg+ insulin + metformin or pioglitazone	Placebo + insulin + metformin or pioglitazone	dap 8.4% pbo 8.4%	- 0.61% + 0.09%	0.7%

Study participants

Four RCTs (8,9,11,12) assessed dapagliflozin. 1,992 participants received dapagliflozin in total; across four RCTs, with trial durations ranging from 12 to 54 weeks. In the single canagliflozin (10) trial, 451 participants received that drug for 12 weeks.

The median base-line HbA1c across the study populations was 8.14% (range 7.7-9.0%), median BMI of 32.7kg/m^2 (range 31.2 – 36.27kg/m^2) and median age of 56.2yrs (range 53 – 59.9yrs).

Interventions

Dapagliflozin was administered orally, with dose ranges from 2.5mg to 20mg, used as once daily preparations.

Canagliflozin dose ranged from 50mg to 300mg administered once daily, with an additional 300mg group administered twice daily.

Here we feel we have focused on doses likely to be used in clinical practice

Background glucose-lowering drugs included insulin, glimepiride, thiazolidinedione (TZD), metformin and insulin, in combination or singly.

Lead in periods

In two studies, (Nauck and Bailey, 8,9) the metformin dose was stabilised during a 2-week lead in period. Strojek (11) stabilised glimepiride over an 8-week lead in.

Wilding (2009) stabilised all OADs over a 10-21 day run in, before fixing doses for the remainder of the study.

Rosenstock (2012) (10), metformin was required to be stabilised for ≥3 months prior to the experiment as an inclusion criteria. The 4-week pre-treatment screening phase was not detailed

Power

All studies included sample size calculations indicating that sufficient numbers of patients were recruited and included in order to detect a 0.5% difference in HbA1c. The Nauck (2011) trial was able to detect 0.35% difference.

Table 2 Summary of trials (selected arms only) and change in HbA1c.

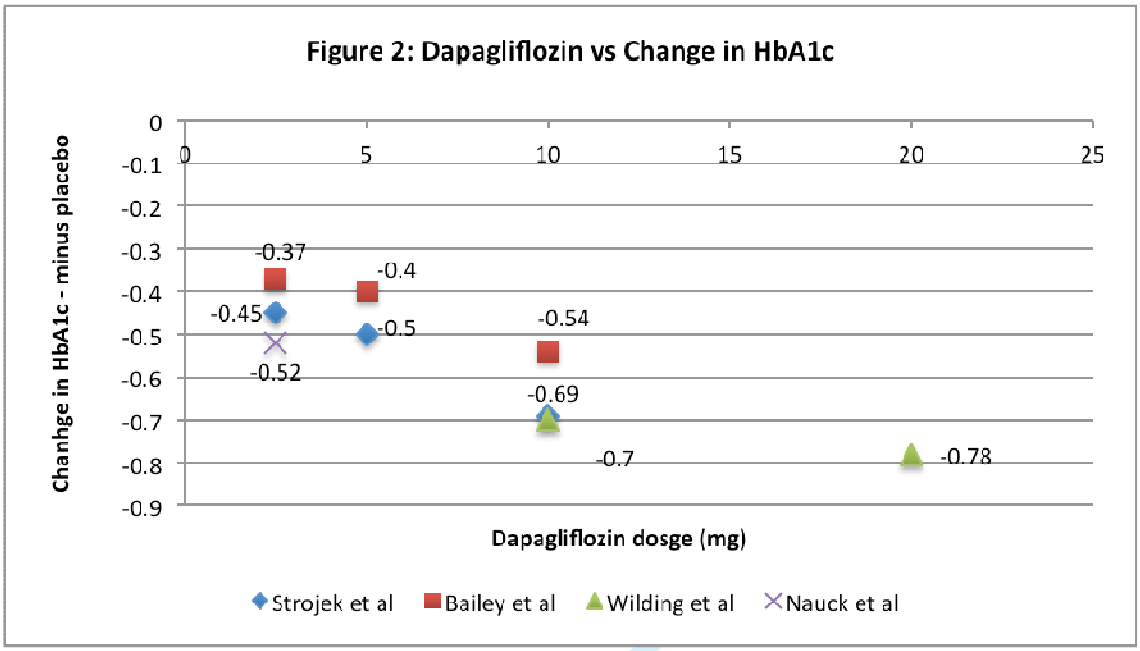
study	SGLT2 inhibitor	Comparator	Baseline HbA1c (SD)	Change in HbA1c (95% CI)	Difference
Bailey 2010	Dapaglifozin 10mg + metformin N=122	Placebo + metformin N= 134	Dap 7.9% (1.0) Pbo 8.1% (0.98)	Dap -0.84% (0.70-0.98 Pbo -0.3% (0.16-0.44)	0.54%
Nauck 2011	Dapagliflozin 2.5mg + metformin N= 406	Glipizide 5mg + metformin N= 408	Dap 7.7% (0.9) Glip 7.7% (0.9)	-0.52% (0.44-0.60 - 0.52% (o,44-0.60)	No difference
Rosenstock 2010	Canagliflozin 300mg once daily N= 64	Sitagliptin N=65	Can 7.7% (0.8) Sita 7.7% (1.0)	-0.92% -0.0.74%	0.18% *
Strojek	Dapaglifozin 10mg + glimepiride 4mg N= 151	Glimepiride 4mg + placebo N= 146	Dap 8.07% (o.79) Pbo 8.15% (0.74)	-0.82% (0.51-0.86 - 0.13% (not given)	0.69%
Wilding 2009	Dapaglifozin 10mg+ insulin + metformin or pioglitazone N= 23	Placebo + insulin + metformin or pioglitazone N=19	Dap 8.4% (0.7) Pbo 8.4%(0.9)	-0.61% (-0.4--0.9) +0.09% (-0.2-+0.4	0.7%

No p value or CI given for difference for sitaglitpin and canaglifozin; no CI for individual changes in Hba1c

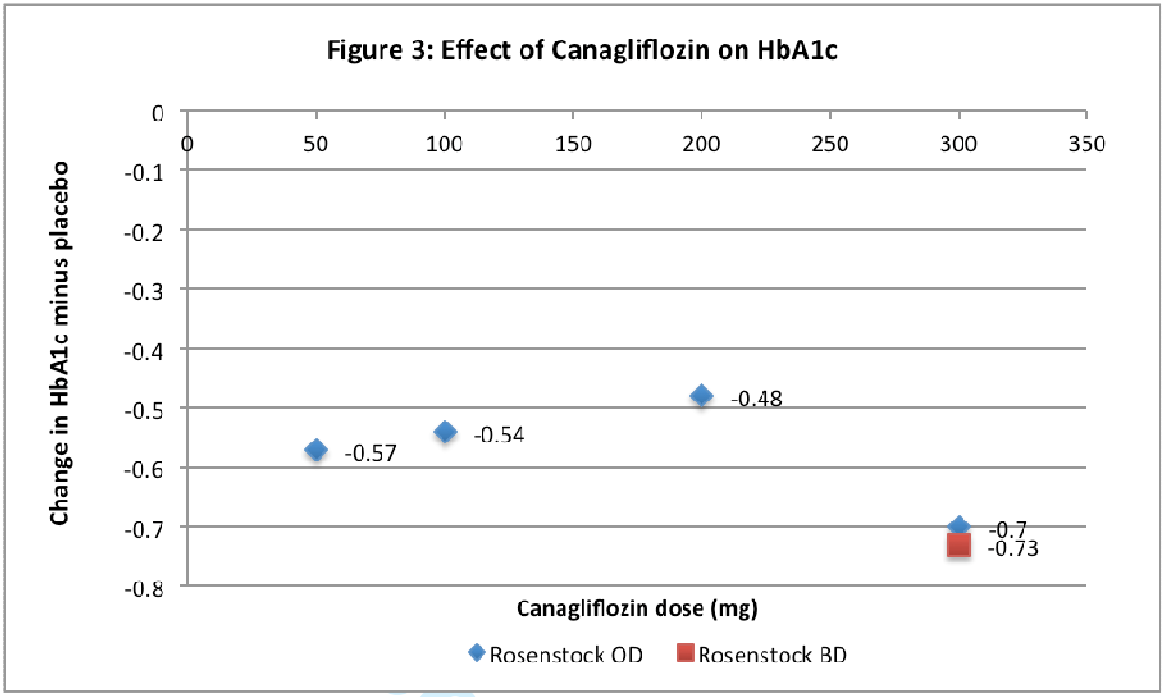
HbA1c Levels

Figure 2 shows change in HbA1c (%) across different SGLT2 inhibitor doses, dapagliflozin from Strojek (2011), Nauck (2011), Bailey (2010) and Wilding (2009). Rosenstock (2012) shows the effect of canagliflozin doses on HbA1c (Figure 3)

Dapagliflozin was shown, as in Fig 2, to reduce HbA1c by between 0.37% and 0.78% when adjusted for changes see by placebo. There was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by 0.52% (Nauck 2011).



Canagliflozin reduced Hba1c in a dose–related manner up to 300mg once daily, with only a small difference (0.18% in HbA1c reduction) between the once daily and twice daily doses at 300mg, as shown in figure 3.



Weight

SGLT2 inhibitors were associated with a significant difference in the change of weight, On 10mg dapagliflozin, weight loss ranged from -1.54kg (Strojek) to -4.50kg (95% CI: -3.5 to -5.5) (Wilding), compared to a reduction of +1.9kg (95% CI: 0.9 to 2.9) on placebo. The lowest reduction due to SGLT2 was reported by Strojek, a non-significant reduction of -0.46kg (95% CI -1.08 to 0.15) with 2.5mg dapagliflozin.

Minor reductions in weight were reported for some comparators; OAD + insulin + placebo (-1.9kg); glimepiride + placebo (-0.72Kg, metformin alone (-0.9kg).

Rosenstock (2012) suggests that for weight change, there was no difference between canagliflozin 300mg once daily and twice daily.

Wilding (2009) also recorded waist circumferences during the study, finding on average, a reduction of -1.7cm, -2.7 and -2.5cm in 2.5mg, 5mg and 10mg dapagliflozin groups, compared to -1.3cm in the placebo.

Systolic Blood Pressure

In placebo-controlled trials, dapagliflozin produced a significant reduction in systolic blood pressure at all doses, with an effect covering a range from -2.1 mmHg to -7.2 mmHg, compared to reductions of 0.2 to 1.2mmHg for placebo. The greatest reduction (-7.2 mmHg standard error (SE), (2.5)) was reported by Wilding (2009) from dapagliflozin 10mg, but it should be noted that there were also changes in insulin dosage at this level. Rosenstock (2012) reported a systolic blood pressure reduction due to canagliflozin from -0.9mmHg (±1.7 SE) with 50mg to -4.9mmHg (±1.5 SE) from 300mg OD compared with placebo of -1.3mmHg (±1.5 SE)

Fasting Plasma Glucose (FPG)

A significant change in FPG was seen in all dapagliflozin groups compared to placebo, with a range of -0.13 to -1.58 mmol/L (unadjusted for placebo) for SGLT2 inhibitors against +0.09 to -0.33mmol/L range for placebo, allowing a maximum reduction of -1.25 mmol/L to be attributed to 10mg dapagliflozin when given as an addition to glimepiride demonstrated by Strojek (2011).
The reductions in FPG rose with SGLT2 dosage; as seen above with the 10mg dapagliflozin dose. Rosenstock (2012) further supported this by showing reductions in FPG from -0.9 to -1.8mmol/l across the 50 to 300mg canagliflozin dosage range, but with no increase in effect above 200mg once daily, indicating a ceiling of efficacy.

Adverse events

Urinary and genital tract infection

Nauck (2011) reported a significant increase in both UTI and genital tract infection (GTI) in the dapagliflozin (2.5mg) group – 44 UTIs and 50 GTIs, (10.8% and 12.3% respectively) compared to glipizide (UTI 26, GTI 11) (6.3% and 2.6%). Amongst the other studies reviewed here, no other significant increase in UTI or GTI was seen. Bailey (2010) suggests that there is no dose related effect in terms of incidence of UTI and GTI for dapagliflozin, demonstrating no difference between dapagliflozin and placebo, with (11/7) (8.20/5.22%) UTI/GTI cases respectively for placebo vs 2.5mg, (6/11) (4.4/8.1%), 5mg ((5/18) (3.75/13.53%)) and 10mg (5/12) (3.78/9.0%). Wilding (2009) similarly reports few infections, with placebo (0 and 1 (4.3%)), 5mg (0 and 0) and finally 20mg ((1/5) (4.3/21.7%)). Rosenstock (2012) suggested a significant difference in UTI due to canagliflozin, 4 UTIs vs maximum of 6 from canagliflozin groups, and 1 GTI compared to a maximum of 5 from canagliflozin, with no evidence of a dose response. In all cases the reported, UTI and GTIs were not severe and resolved with simple treatment.

Hypoglycaemia

Compared to placebo, dapagliflozin resulted in a small, but not statistically significant, increase in incidence of all forms of hypoglycaemia across three of the four dapagliflozin studies. Hypoglycaemia, where data permitted, was divided into three categories: severe, moderate and other, corresponding respectively to capillary glucose readings of; <3.0Mmol/L, <3.5<Mmol/L, and ”Symptoms suggestive of hypoglycaemia, but without confirming capillary glucose measurement”. The incidence of all forms hypoglycaemia ranged from 2.2% (Bailey 2010 with 2.5mg dapagliflozin and metformin) to 30.4%. (Wilding 2009, 10mg dapagliflozin + OAD + insulin).

Wilding (2009), 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. Strojek reported a small, dose independent, increase in hypoglycaemia from dapagliflozin 2.5mg, 5mg and 10mg, 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 amongst 592 participants.

Nauck (2011) 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 150 events).

Rosenstock, comparing placebo to canagliflozin, found an increase in hypoglycaemic events, although the severity was not commented on, with an incidence of 7.2% vs 10.7% for 200mg, (1 vs 6 events)

Other Adverse Events

Across all studies, two deaths were reported in dapagliflozin groups, both by Strojek (2011), attributed to cardiopulmonary arrest, and pulmonary embolism after ischaemic stroke respectively. Neither event was considered to be the result of the study medication.
Three deaths were also reported by Nauck (2011) in the glipizide placebo group, none in the SGLT2 group.
Wilding (2009) noted one occurrence of renal failure reported in the dapagliflozin group
No deaths were reported by Rosenstock (2012)

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:

i) Reducing HbA1c
ii) Improving weight loss in conjunction with advice on lifestyle and diet
iii) Lowering systolic blood pressure
iv) Decreasing FPG levels

Given the mechanism of action of the SGLT2 receptor inhibitors, incidence and severity of hypoglycaemia would be expected to lower (13). Nauck (2011) 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 10mg once daily, since there appears to be little additional benefit from increasing the dose to 20mg. However we have, at present, only one study evaluating the 20mg 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
- The sulphonylureas
- Pioglitazone
- Acarbose
- The meglitinide analogues, nateglinide and repaglinide
- The GLP-1 analogues
- The DPP-4 inhibitors

- The 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 co-morbidities
- Ease of use, by oral administration rather than injection
- Cost

The fear of hypoglycaemia can have a significant impact on the patient's quality of life. 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 I diabetes.

Limitations of studies reviewed

There are no long-term data on SGLT2 side effects, both in terms of rare complications yet to be established, but also on the long-term effects of significant glycosuria on the urinary tract.

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 beta cell capacity.

Musso et al (2010) (14) produced an early systematic review into SGLT2 inhibitors that included 151 articles. The main reason for the difference in number of studies between our own review and that of Musso et al, is our focus is towards a very real world use of SLGT2 inhibitors. We excluded studies of less than 8 weeks in duration, whilst Musso et al analysed studies as short as 2 weeks. In addition, Musso et al included studies with SGLT2 inhibitors are primary intervention, whilst this study has only looked at SGLT2 inhibitors as in combination therapy.

Musso et al reach similar conclusions to our own, namely that SLGT2 inhibitors are effective at reducing HbA1c and fasting plasma glucose levels and BMI, whilst also observing a reduction in serum uric acid and blood pressure.

They come to similar conclusions about a ceiling of effectiveness for dapagliflozin doses of approximately 10-20mg/d

Musso et al conclude there is an increased risk of UTI with SGLT2 inhibitor, with an odds ratio of 1.34. In the present review, numbers of such infections were small in most studies. In the largest study, Nauck and colleagues reported more UTIs with dapagliflozin 2.5mg, 11% (95% CI 7.8 to 14.2%) versus 6% (3.6 to 8.4%) on placebo.

The US Food and Drug Administration (FDA) (15) reviewed dapagliflozin in July 2011. They felt unable to approve it without additional safety data, mainly because of concerns about bladder and breast cancer. In the studies 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 amongst 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 9 to 6 against approval.

Conclusion

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.

Competing interests of authors

None

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Contributions. Rachel Court carried out literature searches. All authors helped design the data extraction form. Christine Clar and James Gill extracted data. James Gill and Norman Waugh drafted the article which has been approved by all authors.

References

1. Diabetes UK,
Diabetes in the UK 2010: Key statistics on Diabetes
http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf
(Accessed October 1st 2011)

2. Mokdad AH, Ford ES, Bowman BA, Dietz W, Vinicor F, Bales V, Marks J.
Prevalence of Obesity, Diabetes, and Obesity-Related Health Risk Factors, 2001
A. JAMA. 2003; 289:76-79..1

3. Stone PH, Muller JE, Hartwell T.
The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis.

J. *Am Coll Cardiol.* 1989; 14:49–57

4. Santer R., Kinner M., Lassen CL., Schenppenheim R, Eggert P, Bald M, et al
Molecular Analysis of the SGLT2 Gene in Patients with Renal Glucosuria.
JASN 2003; 14: 2873-2882

5. Hanefeld M.
Dapagliflozin, an SGLT2 inhibitor, for diabetes.
Lancet 2010; 375:2196-2198

6. Higgins J. and Green S.
Cochrane Handbook for Systematic Reviews of Interventions (2008)
The Cochrane Collaboration. http://www.cochrane.org/training/cochrane-handbook
(Accessed Sept 1st 2011)

7. **Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications.**
Report of a WHO Consultation, WHO/NCD/NCS/99.2 (2000)
http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf
(Accessed Sept 20th 2011)

8. 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

9. Nauck MA, Del Prato S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al
Dapagliflozin Vs Glipizide as Add-on Therapy in Patients with Type 2 diabetes who have inadequate glycaemic control with Metformin
Diabetes care 2011; 34:2015-2022

10. 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 **June 2012** vol. 35 no. 6 **1232-1238**

11. 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 Obes. Metab. 2011; 13(10):928-938

12. 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

13. Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L, et al
Dapagliflozin a novel SGLT2 inhibitor induces dose-dependent glucosuria in healthy subjects.
Clin. Pharmacol Ther. 2009; 85:520-6

14. Musso G, Gambino R, Cassader M, Pagano G.
A novel approach to control hyperglycaemia in type 2 diabetes: Sodium glucose co-transport (SGLT) inhibitors. Systematic review and meta-analysis of randomised trials.
Annals of Medicine, 2011, Early On-line 1-19

15. Food and Drug Adminstration. Center for Drug Evaluation and Research
Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee
July 19, 2011

Appendix

<table>
<tr><td colspan="4">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]</td><td>Funding source: Astra-Zeneca and Bristol-Myers-Squibb
SGLT2 Inhibitor Vs. metformin</td></tr>
<tr><td colspan="5">Aim: Determine if dapagliflozin, lowers HbA1c in type 2 diabetes in patients with inadequate HbA1c control with metformin</td></tr>
<tr><td>Study Particulars</td><td colspan="4">Multi Centre: 81
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 RCT, double blind, placebo controlled

Primary outcome: Change from baseline in HbA1c at week 24

Secondary outcomes:
At 1 week, change in fasting plasma glucose
At 24 weeks changes in:
• Fasting plasma
• Glucose concentration
• No. with baseline HbA1c of 9% or more.
• Proportion of patients achieving a therapeutic HbA1c, and
• Total bodyweight..
• Change from baseline in bodyweight, and decreases in bodyweight of 5% or more.</td></tr>
<tr><td>Participant Criteria</td><td colspan="4">N: 534 analysed
Inclusion criteria: participants aged between 18 years and 77; Type 2 diabetes, BMI <45kg/m2, HbA1c 7-10.0%; fasting C-peptide >0.34ng/ml, taking stable dose metformin>1500mg

Exclusion criteria (taken from paper): (serum creatinine 133 µmol/L or more for men or 124 µmol/L or more for women (consistent with metformin labeling); urine albumin/creatinine ratio more than 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); and systolic blood pressure 180 mm Hg or more or diastolic blood pressure 110 mm Hg or more. Any significant other systemic disease

Lead in period: 2 weeks, single blind, to assess compliance with placebo, patients randomised successful completion. Metformin dose stabilised to >1500mg</td></tr>
<tr><td>Quality</td><td colspan="4">Study Quality: medium – See Quality table for further information</td></tr>
<tr><td>Participant baseline data</td><td>Group 1 (n analysed=134):
Placebo OD + metformin,</td><td>Group 2 (n= 135):
2.5mg dapagliflozin OD, metformin</td><td>Group 3 (n= 133):
5mg dapagliflozin OD, metformin</td><td>Group 4 (n= 132):
10mg dapagliflozin OD, metformin</td></tr>
<tr><td></td><td>Age: 53.7 SD 10.3 years
Sex: 55% Male
BMI (KG/M^2): 31.8 SD 5.3
HbA1c (%): 8.11% SD 0.96
Duration of Diabetes: 5.8 SD 5.1</td><td>Age: 55.0 SD 9.3 years
Sex: 51% Male
BMI (KG/M^2): 31.6 SD 4.8
HbA1c (%): 8.96% SD 2.39
Duration of Diabetes: 6.0 SD 6.2</td><td>Age: 54.3 SD 9.4 years
Sex: 50% Male
BMI (KG/M^2): 31.4 SD 5.0
HbA1c (%): 8.17% SD 1.0
Duration of Diabetes: 6.4 SD 5.8</td><td>Age: 52.7 SD 9.9 years
Sex: 57% male
BMI (KG/M^2): 31.2 SD 5.1
HbA1c (%): 7.92% SD 0.82
Duration of Diabetes: 6.1 SD 5.4</td></tr>
</table>

	FPG (mmol/l): 9.19 SD 2.57 **Systolic BP:** 127.7 SD 14.6		**FPG (mmol/l):** 8.96 SD 6.2 **Systolic BP:** 126.6 SD 14.5		**FPG (mmol/l):** 9.39 SD 2.7 **Systolic BP:** 126.9 SD 14.3		**FPG (mmol/l):** 8.66 SD 2.15 **Systolic BP:** 126.0 SD 15.9	
Outcome (change from baseline at study end)								
	Group 1 (n analysed=134): Placebo OD + metformin,		**Group 2 (n= 135):** 2.5mg dapagliflozin OD, metformin		**Group 3 (n= 133):** 5mg dapagliflozin OD, metformin		**Group 4 (n= 132):** 10mg dapagliflozin OD,	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ HbA1c (%)	-0.3	-0.44 to -0.16	-0.67	-0.81 to -0.53	-0.70	-0.85 to -0.56	-0.84	-0.98 to -0.70
Δ Weight (kg)	-0.9	-1.4 to -0.4	-2.2	-2.8 to -1.8	-3.0	-3.5 to -2.6	-2.90	-3.3 to -2.4
Δ FPG (mmol/L)	-0.33	-0.62 to -0.04	-0.99	-1.28 to -0.69	-1.19	-1.49 to -0.90	-1.3	-1.60 to -1.00
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Δ SBP (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	**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):** 2.5mg dapagliflozin OD, metformin		**Group 3 (n= 133):** 5mg dapagliflozin OD, metformin		**Group 4 (n= 132):** 10mg dapagliflozin OD,	
Specific Events	UTI: n= 11, GTI n = 7, HypoT n=1, HypoG n=4,		UTI: n= 6 GTI n = 11 HypoT n=0, HypoG n=3		UTI: n= 10, GTI n = 18 HypoT n=2, HypoG n=5,		UTI: n= 16, GTI n =12, HypoT n=0, HypoG n=5	
	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	
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits							

Nauck MA, Del Prato S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al **Dapagliflozin Vs Glipizide as Add-on Therapy in Patients with Type 2 diabetes who have inadequate glycaemic control with Metformin** Diabetes care 2011. 34:[2015-2022]		**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 Inhibitor + metformin vs metformin + glipizide**
Aim: Compare efficacy, safety and tolerability of dapagliflozin with glipizide, in patients with type 2 diabetes poorly controlled with monotherapy		
Study Particulars	**Multi Centre:** 95 sites across 10 countries World-wide **Duration of intervention**: 52 weeks **Duration of run in**: 2 weeks **Followup:** on completion of 52 weeks, a 156 week long-term study **Design:** 2-arm parallel group, RCT. **Primary outcome:** Absolute change from baseline in HbA1c at week 52 **Secondary outcomes:** - Change in total body weight - Proportion with hypoglycaemic episode - Proportion if ≥ 5% total weight loss.	
Participant Criteria	**N:** 801 analysed **Inclusion criteria:** participants aged 18 years and older; inadequately controlled type 2 diabetes, BMI ≤45kg/m2, HbA1c >6.5 and ≤10%; fasting C-peptide ≥0.33nmol/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, fasting plasma glucose ≤15mmol/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 x upper limit of normal; total bilirubin >34 µmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSH; systolic blood pressure ≥180mmHg and/or diastolic blood pressure ≥110 mmHg; significant other disease.	
Interventions	**Intervention 1:** 2.5mg dapagliflozin + metformin **Intervention 2:** 5mg glipizide + metformin **Lead in period:** 2 weeks, single blind placebo lead in prior to randomization. **All groups:** Patients randomly assigned to double blind therapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All patients maintained metformin	
Quality	**Study Quality:** medium – See Quality table for further information	
Participant baseline data	**Group 1** (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin	**Group 2 (**start n= 408, analysed n= 401): 5mg glipizide + metformin
	Age: 58 SD 9 years **Sex:** 55.3% Male **BMI (KG/M^2):** 31.7 SD 5.1 **≥ 25 kg/m^2**: 95%% **≥ 30 kg/m^2:** 57% **HbA1c (%):** 7.7% SD 0.9 **Duration of Diabetes:** 6 SD 5	**Age:** 59 SD 10 years **Sex:** 54.9§% Male **BMI (KG/M^2):** 31.2 SD 5.1 **≥ 25 kg/m^2**: 90.7% **≥ 30 kg/m^2:** 55.4% **HbA1c (%):** 7.7% SD 0.9 **Duration of Diabetes:** 7 SD 6

	FPG (mmol/l): 9.0 SD 2.1		**FPG (mmol/l):** 9.1 SD 2.3	
Outcome (change from baseline at study end)				
	Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin		**Group 2 (**start n= 408, analysed n= 401): 5mg glipizide + metformin	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ HbA1c (%)	-0.52	-0.60 to -0.44	-0.52	-0.60 to -0.44
Δ Weight (kg)	-3.22	-3.56 to -2.87	+1.44	+1.44
Δ FPG (mmol/L)	-1.24	-1.42 to -1.07	-1.04	-1.22 to -0.98
	Mean	**SD**	**Mean**	**SD**
Δ SBP (mmHg)	-4.3	-	-+0.8	-
HbA1c	-	-	-	-
Adverse Events	**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 ≥3%** 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 =*** *n=318* ***Group 2 =*** *n=318* No deaths in Dapagliflozin group 3 deaths in Glipizide group
	Group 1		**Group 2**	
Specific Events	UTI: n=44, GTI n = 50, HypoM n= 0 HypoS n= 7 HypoO, n=7 Events Leading to Discontinuation, n=0		UTI: n=26, GTI n = 11, HypoM n= 3 HypoS n= 147 HypoO, n=40 Events Leading to Discontinuation, n=6	
	Diarrhoea n= 19 Nausea n= 14 Vulvovaginal mycotic infection n= 14 Back pain n= 19 Nasopharyngitis n= 43 Cough n= 15 Influenza n= 30 Pain in extremity 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 Pain in extremity n= 21 Upper resp. Tract Infection n= 17 Headache n= 17 Hypertension n= 35	
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits			

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 **June 2012** vol. 35 no. 6 **1232-1238**	**Funding source:** *Johnson and Johnson* **Placebo + metformin** **vs** **SGLT2 Inhibitor + metformin OD** **Vs** **SGLT2 inhibitor BD + metformin OD** **Vs** **sitaglipitin OD + metformin**
Aim: Assess the safety, tolerability and efficacy of an alternative SGLT2 inhibitor Canagliflozin and remaining beta cell function, in DM type 2 patients who have inadequate glycaemic control using metformin as a monotherapy.	
Study Particulars	**Multi Centre:** 12 countries at 85 sites **Duration of intervention**: 12 weeks **Duration of run in**: 4 week **Followup:** 2 week **Design:** 7-arm parallel group, RCT. Double blind, placebo controlled trial looking at metformin, canagliflozin 50, 100, 200, 300mg OD and 300mg BD, and sitaglipitin 100mg **Primary outcome:** Change from baseline in HbA1c **Secondary outcomes:** Change in fasting plasma glucose at week 12, change in weight, overnight glucose-to-creatinine ratio, change in proportion of subjects with HbAc <7.0% and<6.5% after 12 weeks. Finally the assessment of the loss of beta cell function measured using HOMA2-B% derived from plasma glucose and C peptide
Participant Criteria	**N:** 451 randomised, 402 analyzed against primary outcome **Inclusion criteria:** 18-65yr old, diabetes type 2 for >3months, HbA1c level ≥7% and ≤10.5% People with type 2 diabetes with inadequate glycaemic control using metformin monotherapy, stable body weight, BMI 25-45, serum creatinine <1.5mg/dl for men, <1.4mg/dl for women **Exclusion criteria (taken from paper):** HbA1c ≥10.6%, metformin dose of ≤1500mg/day, unstable body weight, BMI≤25 ≥45, serum creatinine ≥1.4 **Lead in period:** 3-4 weeks
Quality	**Study Quality:** Medium – See Quality table for further information
Participant baseline data	**Age:** 53 **Sex:** male 52% **BMI (KG/M^2):** 31.5 **HA1c (%):** 7.7% **Duration of Diabetes:** - **FPG (mmol/l):** 9.0 **Systolic BP:**
Outcome (change from baseline at study end)	

	Group 1 placebo + metformin (n=55)		**Group 2** canagliflozin 50mg + Metformin (n=59)		**Group 3** canagliflozin 100mg + metformin (n=59)		**Group 4** canagliflozin 200mg + metformin (n=56)	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ HbA1c (%)	-0.22	-	-0.79	-	-0.76	-	-0.70	-
Δ Weight (kg)	-1.1	-	-1.2	-	-1.5	-	-1.6	-
Δ FPG (mmol/L)	+0.19	-	-0.9	-	-1.4	-	-1.8	-
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Δ SBP (mmHg)	-1.3	1.5	-0.9	1.7	+1.0	1.3	-2.1	1.8
HbA1c	7.5	0.96	7.2	0.88	7.1	0.85	6.9	0.68
	Group 5 canagliflozin 300mg + metformin (n=56)		**Group 6** canagliflozin 300mg BD + metformin (n=57)		**Group 7** sitagliptin + metformin (n=60)			
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**		
Δ HbA1c (%)	-0.92	-	-0.95	-	-0.74	-		
Δ Weight (kg)	-2.3	-	-2.3	-	+0.5	-		
Δ FPG (mmol/L)	-1.8	-	-1.7	-	-0.69	-		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Δ SBP (mmHg)	-4.9	1.5	-3.6	1.4	-0.8	1.4		
HbA1c	6.8	0.82	6.8	0.72	6.9	0.92		
Adverse Events	**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 ≥3%** UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia		***At least one or more adverse event*** ***Group 1 =*** *n=11* ***Group 2 =*** *n=25* ***Group 3 =*** *n=26* ***Group 4 =*** *n=24* ***Group 5 =*** *n=19* ***Group 6 =*** *n=25* ***Group 7 =*** *n=16*			
Specific Events	**Group 1**		**Group 2**		**Group 3**		**Group 4**	
	UTI: n=4, GTI n = 1 Events Leading to Discontinuation, n=1 Hypo = 1		UTI: n=3, GTI n = 5, Events Leading to Discontinuation, n=1 Hypo = 0		UTI: n=2, GTI n = 4, Events Leading to Discontinuation, n=3 Hypo = 1		UTI: n=6, GTI n = 2, Events Leading to Discontinuation, n=1 Hypo = 4	
	Headache n= 2 Vulvovaginal mycotic infection n= 0 Nausea n= 0 Nasopharyngitis n= 2 Diarrhoea n= 2 Pollakiuria n = 1		Headache n= 1 Vulvovaginal mycotic infection n= 4 Nausea n= 4 Nasopharyngitis n= 5 Diarrhoea n= 1 Pollakiuria n = 1		Headache n= 5 Vulvovaginal mycotic infection n= 2 Nausea n= 1 Nasopharyngitis n= 0 Diarrhoea n= 1 Pollakiuria n = 3		Headache n= 2 Vulvovaginal mycotic infection n= 4 Nausea n= 1 Nasopharyngitis n= 0 Diarrhoea n= 0 Pollakiuria n = 1	

	A/E associated with hypotension n= 1	A/E associated with hypotension n= 0	A/E associated with hypotension n= 4	A/E associated with hypotension n= 3
	Group 5	**Group 6**	**Group 7**	
	UTI: n=2, GTI n = 2, Hypo = 0 Events Leading to Discontinuation, n=2	UTI: n=3, GTI n = 4, Hypo = 2 Events Leading to Discontinuation, n=2	UTI: n=1, GTI n = 1, Hypo = 3 Events Leading to Discontinuation, n=0	
	Headache n= 3 Vulvovaginal mycotic infection n= 1 Nausea n= 3 Nasopharyngitis n= 1 Diarrhoea n= 2 Pollakiuria n = 2 A/E associated with hypotension n= 1	Headache n= 1 Vulvovaginal mycotic infection n= 3 Nausea n= 5 Nasopharyngitis n= 1 Diarrhoea n= 3 Pollakiuria n = 0 A/E associated with hypotension n= 1	Headache n= 1 Vulvovaginal mycotic infection n= 1 Nausea n= 1 Nasopharyngitis n= 3 Diarrhoea n= 2 Pollakiuria n = 2 A/E associated with hypotension n= 1	
	Genital tract infections: *3-8% canagliflozin arms* *2% placebo* *2% sitagliptin*	***UTI*** *3-9% canagliflozin arms* *6% placebo* *2% sitagliptin*	***Hypoglycaemia*** *0-6% canagliflozin arms* *2% placebo* *5% sitagliptin*	
	All AE were seen to be non-dose dependent **After 12 weeks no "safety signals" (undefined) in lab studies, ECG or vital signs were seen in Canagliflozin arms** **Similar incidences of discontinuation due to adverse events, although number not specified** **Number of severe adverse events not given**			
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activties (MedDRA v12.1) via patient questionnaire and active questioning during visits			

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 Obes. Metab. 2011 13(10):[928-938]	**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **2.5, 5, 10mg SGLT2 Inhibitor (dapagliflozin) vs 4mg glimepiride**
Aim: To determine 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	
Study Particulars	**Multi Centre:** 84 sites across 7 countries **Duration of intervention**: 52 weeks **Duration of run in**: 2 weeks **Follow-up:** on completion of 52 weeks, a 156 week long-term study

	Design: 2-arm parallel group, double-blind RCT **Primary outcome:** Absolute HbA1c change from baseline to week 24 **Secondary outcomes:** - Total body weight after 24 weeks - Change from baseline after week 24 in post challenge plasma glucose (2hrs) following oral glucose tolerance - Proportion of patients with HBA1c <7% after 24 weeks - Total body weight from baseline if BMI ≥27kg/m^2 - FPG from baseline after 24weeks			
Participant Criteria	**N:** 592 analyzed **Inclusion criteria:** Participants aged 18 years and older; inadequately controlled type 2 diabetes, BMI ≤45kg/m^2, HbA1c of ≥7 to ≤10.0%; 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, fasting plasma glucose ≤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 x upper limit of normal; total bilirubin >34 µmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSH; SBP ≥180 mmHg and/or DBP ≥110 mmHg. Any significant other systemic disease			
Interventions	**Intervention 1:** placebo plus 4 mg/day glimepiride **Intervention 2:** 2.5 mg/day dapagliflozin plus 4 mg/day glimepiride **Intervention 3:** 5 mg/day dapagliflozin plus 4 mg/day glimepiride **Intervention 4:** 10 mg/day dapagliflozin plus 4 mg/day glimepiride **Lead in period:** 1 week for inclusion/exclusion review for those switched to 4 mg/day glimepiride **All groups:** dapagliflozin double-blind, glimepiride open label; glimepiride allowed to be down-titrated to 2 mg/day or discontinued in case of hypoglycaemia, no up-titration allowed; in case of inadequate glycaemic control, patients could receive open-label rescue therapy of metformin, pioglitazone or rosiglitazone; all patients received dietary and lifestyle counseling and patients with BMI ≥27 kg/m^2 received advice regarding reducing caloric intake and increasing physical activity			
Quality	**Study Quality:** Medium – See Quality table for further information			
Participant baseline data	**Group 1 (n= 146)** Placebo + glimepiride	**Group 2 (n= 154)** 2.5mg dapagliflozin + glimepiride	**Group 3 (n= 145)** 5mg dapagliflozin + glimepiride	**Group 4 (n= 151)** 10mg dapagliflozin + glimepiride
	Age (years): 60.3 SD 10.16 **Sex:** 49% male **BMI (kg/m^2)** **≥ 25 kg/m^2**: 86.2% **≥ 30 kg/m^2:** 45.5% **HbA1c (%):** 8.15 SD 0.74 **Duration of diabetes (years):** 7.4SD 5.7 **FPG (mmol/L):** 9.58 SD 2.07 **Systolic BP (mmHg):** 133.3	**Age (years):** 59.9.3 SD 10.14 **Sex:** 50% male **BMI (kg/m^2)** **≥ 25 kg/m^2**: 84.4% **≥ 30 kg/m^2:** 48% **HbA1c (%):** 8.11, SD 0.75 **Duration of diabetes (years):** 7.7 SD 6.0 **FPG (mmol/L):** 9.56, SD 2.13 **Systolic BP (mmHg):** 134.6	**Age (years):** 60.2 SD 9.73 **Sex:** 50% male **BMI (kg/m^2)** **≥ 25 kg/m^2**: 78% **≥ 30 kg/m^2:** 50% **HbA1c (%):** 8.12 SD 0.78 **Duration of diabetes (years):** 7.4 SD 5.7 **FPG (mmol/L):** 9.68 SD 2.12 **Systolic BP (mmHg):** 130.9	**Age (years):** 58.9 SD 8.32 **Sex:** 43.7% male **BMI (kg/m^2)** **≥ 25 kg/m^2**: 79.4% **≥ 30 kg/m^2:** 45.% **HbA1c (%):** 8.07 SD 0.79 **Duration of diabetes (years):** 7.2 SD 5.5 **FPG (mmol/L):** 9.55 SD 2.04 **Systolic BP (mmHg):** 133.8 SD 15

Outcome (change from baseline at study end)								
	Group 1 (n= 146) Placebo + glimepiride		**Group 2 (n= 154)** 2.5mg dapagliflozin + glimepiride		**Group 3 (n= 145)** 5mg dapagliflozin + glimepiride		**Group 4 (n= 151)** 10mg dapagliflozin + glimepiride	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ from baseline HbA1c (%)	-0.13	-	-0.58	-0.61 to -0.27	-0.63	-0.67 to -0.32	-0.82	-0.86 to -0.51
Δ from baseline Weight (kg)	-0.72	-	-1.18	-1.08 to +0.15	-1.56	-1.47 to -0.21	-2.26	-2.17 to -0.92
Δ from baseline FPG (mmol/L)	-0.33	-	-2.08	-2.50 to -1.00	-1.78	-2.20 to -0.68	-1.94	-2.34 to 0.87
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Absolute Δ SBP from placebo (mmHg)	-1.20	-	-4.7	-6.1 to -0.9	-4.0	-5.5 to -0.2	-3.8	-6.4 to -1.2
HbA1c	-	-	-	-	-	-	-	-
Adverse Events	**General events – where frequency is ≥3% in any group** UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia				Hypoglycaemia defined as blood sugar <70mg/dl)		***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 2.5mg 1 death in Dapagliflozin 10mg	
	Group 1 (n= 146) Placebo + glimepiride		**Group 2 (n= 154)** 2.5mg dapagliflozin + glimepiride		**Group 3 (n= 145)** 5mg dapagliflozin + glimepiride		**Group 4 (n= 151)** 10mg dapagliflozin + glimepiride	
Specific Events	UTI: n=9, GTI n = 1, ≥ 1Hypo n= 7		UTI: n=6, GTI n = 6, ≥ 1Hypo n= 11		UTI: n=10, GTI n = 9, ≥ 1Hypo n= 11		UTI: n=8, GTI n = 10, ≥ 1Hypo n= 12	
	Bronchitis n= 4 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		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= 4 Hypertension n= 2	
Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activties (MedDRA v12.1) via patient questionnaire and active questioning during visits							

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]			**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 Inhibitor + patients own oral antidiabetic drugs (OAD) Vs insulin + OAD**
Aim: Determine if Dapagliflozin, lowers HBA1c in Type 2 diabetes in patients with type 2 diabetes poorly controlled with high insulin doses plus oral antidiabetic agents			
Study Particulars	**Multi Centre:** 26 sites (USA and Canada) **Duration of intervention**: 52 weeks **Duration of run in**: 2 weeks **Follow-up:** on completion of 52 weeks, a 156 week long-term study **Design:** 2-arm parallel group, RCT **Primary outcome:** Change from baseline in HbA1c at week 12 **Secondary outcomes:** - Change from baseline FPG - Change in total daily requirement of insulin - Percentage of patients with change in HbA1c >0.5% - Percentage of end patients with final HbA1c <7%		
Participant Criteria	**N:** 65 analysed **Inclusion criteria:** Participants aged between 18 years and 75; type 2 diabetes, BMI ≤45 kg/m^2, HbA1c of 7.5-10.0%; taking stable dose metformin (≥1000mg) and/or pioglitazone (≥30mg) for ≥6 weeks and insulin therapy (50 units) ≥12 weeks before enrolment. Fasting C-peptide ≥0.8 ng/ml, serum creatinine <1.5 mg/dl (men) or <1.4 mg/dl (women), and a 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 limits of normal, creatine kinase ≥3 times the upper limits of normal, symptoms of severely uncontrolled diabetes including a history of severe hypoglycemia. Any significant other disease		
Interventions	**Intervention 1:** placebo plus stable dose of insulin sensitizer (metformin and/or pioglitazone) plus insulin (50% of pre-study dose) **Intervention 2:** 10 mg dapagliflozin once daily plus insulin sensitizer and insulin as in intervention 1 **Intervention 3:** 20 mg dapagliflozin once daily plus insulin sensitizer and insulin as in intervention 1 **All groups:** insulin dose reduced to 50%; diet and exercise programme (American Diabetes Association or similar local guidelines); following lead in period there were no dose adjustments to OADs; insulin could be down-titrated in patients at risk of hypoglycaemia **Lead in period:** 10-21 day to establish reduced insulin dose		
Quality	**Study Quality:** Medium – See Quality table for further information		
Participant baseline data	**Group 1 (n analysed=19):** Placebo, OADs + insulin,	**Group 2 (n= 23):** 10mg dapagliflozin, OADs + insulin,	**Group 3 (n= 23):** 20mg dapagliflozin OD, OADs + insulin,

	Age (years): 58.4 SD 6.5 **Sex:** 69.6% male **BMI (kg/m^2):** 34.8 SD 4.6 **HbA1c (%):** 8.40% SD 0.9 **Duration of diabetes (years):** 7.4SD 5.7 **FPG (mmol/L):** 9.22 SD 2.86 **Systolic BP (mmHg): n/a**		**Age (years):** 55.7 SD 9.2 **Sex:** 54.2% male **BMI (kg/m^2):** 35.5 SD 3.6 **HbA1c (%):** 8.4% SD 0.7 **Duration of diabetes (years):** 11.8 SD 5.8 **FPG (mmol/L):** 8.67 SD 2.17 **Systolic BP (mmHg): n/a**		**Age (years):** 56.1 SD 10.6 **Sex:** 54.2% male **BMI (kg/m^2):** 36.2 SD 4.6 **HbA1c (%):**8.5% SD 0.9 **Duration of diabetes (years):** 11.3 SD 5.6 **FPG (mmol/L):** 8.98 SD 3.06 **Systolic BP (mmHg): n/a**	
Outcome (change from baseline at study end)						
	Group 1 (n analysed=19): Placebo, OADs + insulin,		**Group 2 (n= 23):** 10mg dapagliflozin, OADs + insulin,		**Group 3 (n= 23):** 20mg dapagliflozin OD, OADs + insulin,	
	Mean	**Confidence (95%)**	**Mean**	**Confidence (95%)**	**Mean**	**Confidence (95%)**
Δ HbA1c (%)	+0.09	-0.2 to +0.4	-0.61	-0.9 to -0.4	-0.69	-0.90 to -0.4
Δ Weight (kg)	-1.9	-2.9 to -0.9	-4.50	-5.5 to -3.5	-4.3	-5.3 to -3.3
Δ FPG (mmol/L)	+0.99	+0.08 to +1.90	-0.13	-0.75 to +1.02	-0.53	-1.42 to +0.35
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Δ SBP (mmHg)	-	-	-7.2	-	-6.10	-
HbA1c	8.5	0.8	7.80	0.7	7.80	0.60
Adverse Events	**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=15* ***Group 2 =*** *n=18* ***Group 3 =*** *n=16* *One patient in each group discontinued due to adverse effects*	
Specific Events	**Group 1 (n analysed=19):** Placebo, OADs + insulin,		**Group 2 (n= 23):** 10mg dapagliflozin, OADs + insulin,		**Group 3 (n= 23):** 20mg dapagliflozin OD, OADs + insulin,	
	UTI: n=0, GTI n = 1, HypoT n=n/a, HypoG n=3		UTI: n= 0, GTI n = 0, HypoT n=n/a, HypoG n=7,		UTI: n= 1, GTI n = 5, HypoT n=n/a, HypoG n=6	
	Nausea n= 1 Pollakiuria n= 4 Back pain n= 2 Nasopharyngitis n= 2 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 odema n=2 Abdominal pain n=2 Fatigue n= 1 Influenza n= 1 Pain in extremity n= 1 Upper resp. Tract Infection n= 1	

Safety Assessment	Assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits

Figure 1: search results

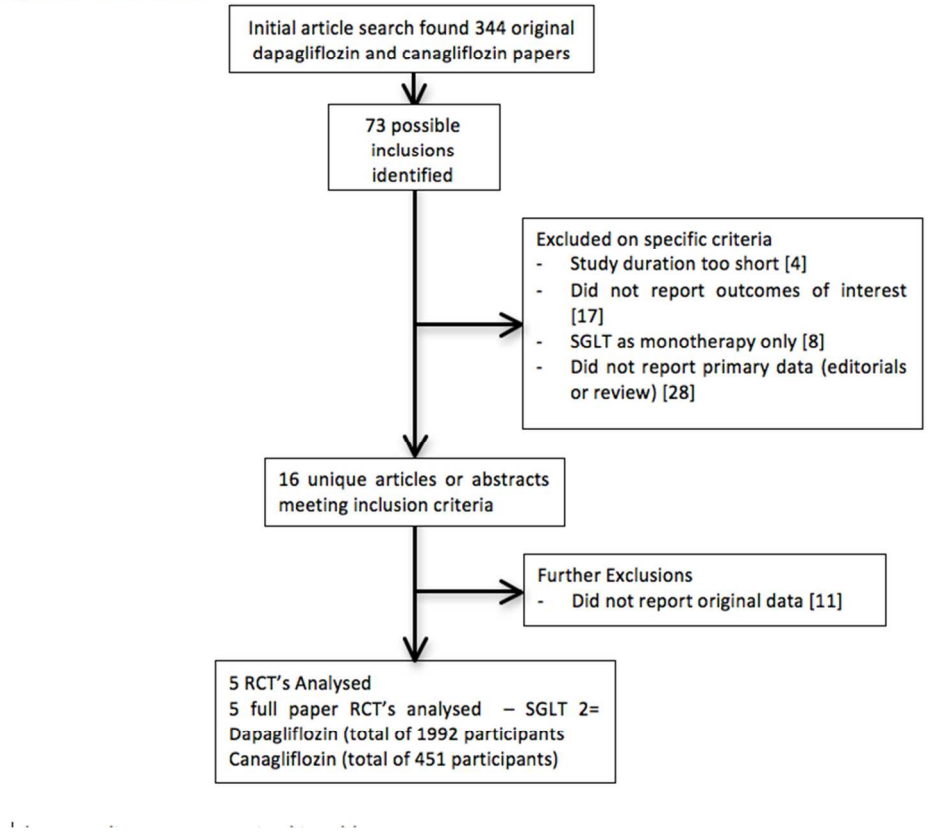

figure 1
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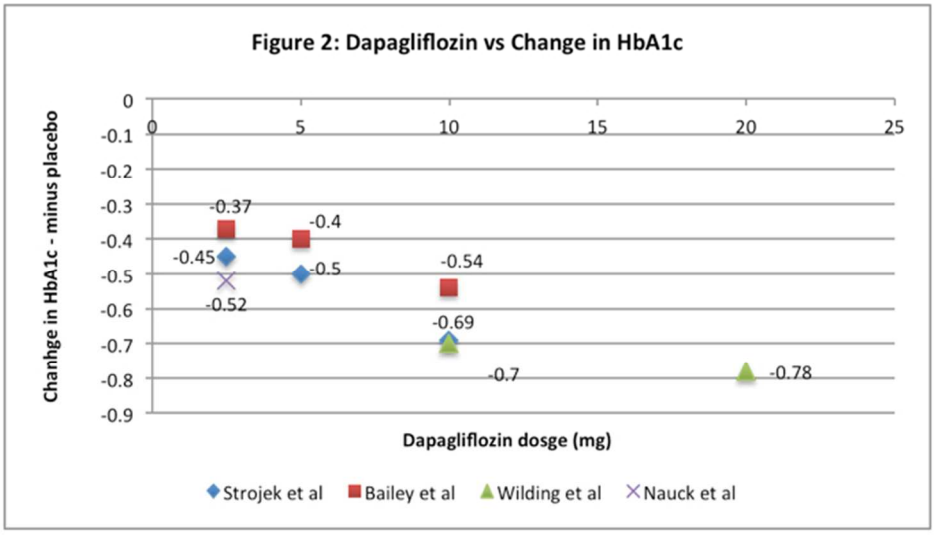
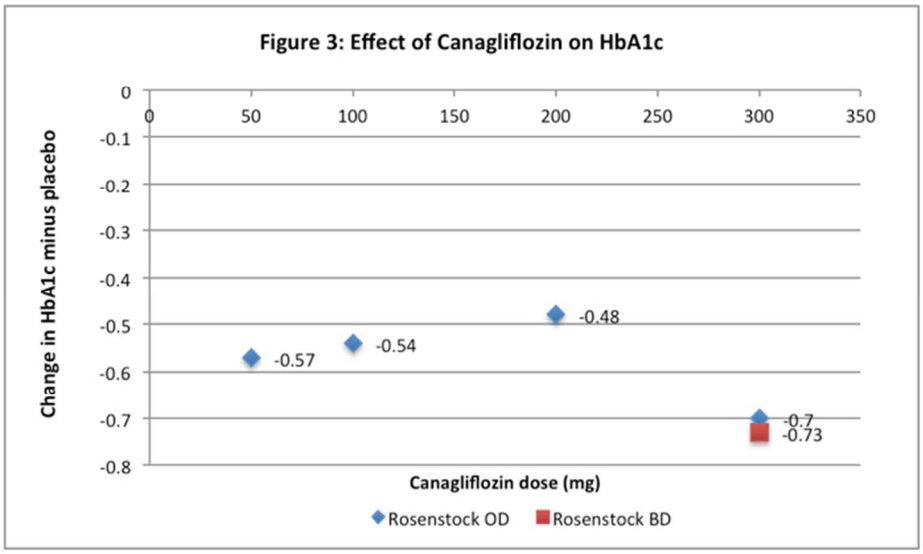


258x143mm (72 x 72 DPI)



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Systematic Review of SGLT2 Receptor Inhibitors in dual or triple therapy in type 2 diabetes

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Title: 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% (WMD, 95% CI -0.67, -0.40) compared to placebo, but there was no difference compared to glipizide. Canagliflozin reduced HbA1c slightly more than sitagliptin (up to -0.21% versus sitagliptin). Both dapagliflozin and canagliflozin led to weight loss (dapagliflozin WMD -1.81 kg (95% CI -2.04, -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 FDA 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.

INTRODUCTION

Type 2 diabetes is one of the most important and prevalent chronic diseases today, with in 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 (NICE), recommend that if lifestyle intervention is insufficient, the first line of drug treatment is metformin, followed by a sulphonylurea, or sometimes a glitazone, before commencing 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 anti-diabetic 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. 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 to 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, e.g. metformin plus SGLT2 versus metformin plus sulphonylurea, and in triple therapy, e.g. 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 control 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 quality of life 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 to 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, effect should not vary by duration of disease. Type 2 diabetes is often a progressive disease with diminishing beta cell capacity.

Interventions

Any use of SGLT2 inhibitors (dapagliflozin, 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 quality of life

- Cardiovascular events

Adverse effects, including hypoglycaemia, urinary tract infection (UTI)

Search methods for identification of studies

We searched the following sources:

- MEDLINE
- MEDLINE in-Process
- EMBASE
- The Cochrane Library, all sections
- NHS HTA
- Science Citation Index Expanded (SCI expanded)
- On-going Trials Registers:
- Clinical trials (www.clinicaltrials.gov)
- Current Control Trials (www.controlled-trials.com/)
- American Diabetes Association – Conference Abstracts
- EASD – 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. 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. SGLT-2 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 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

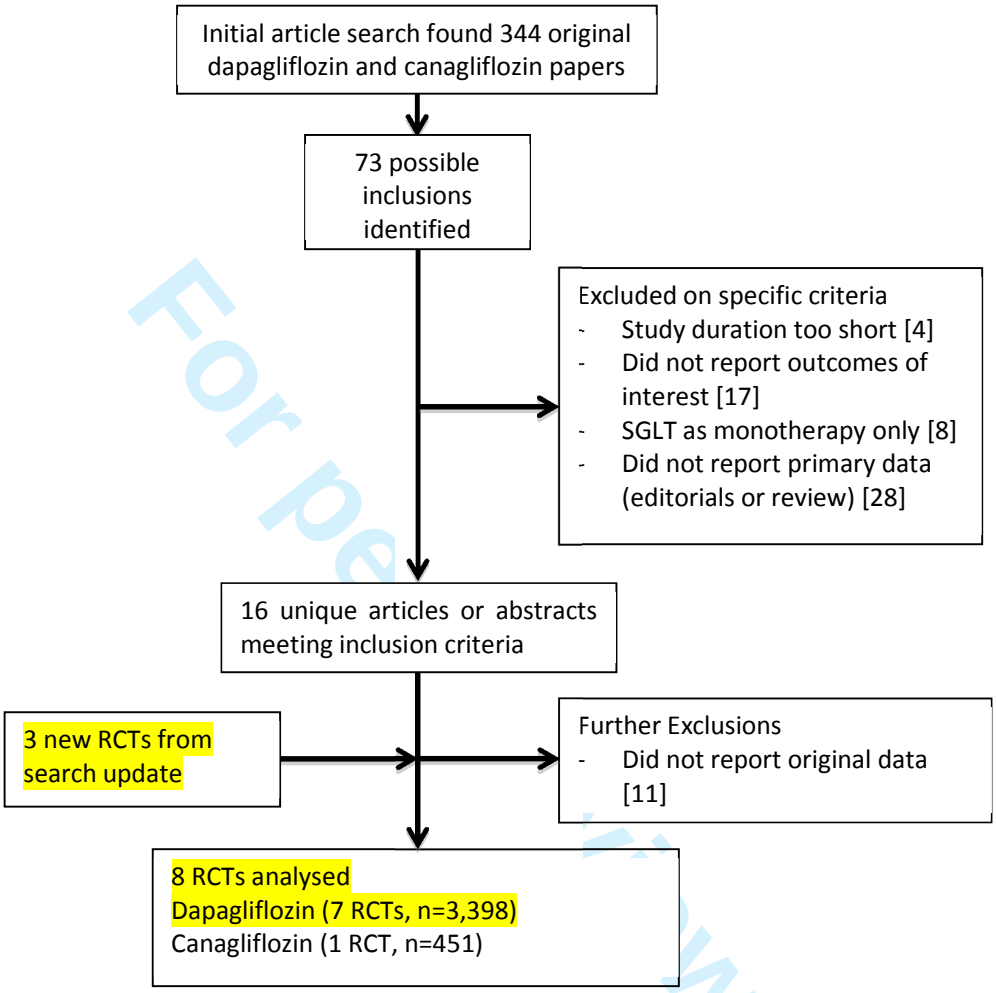
The data analysis has been reported according to the guide set down within the Cochrane Handbook for Systematic Reviews of Interventions.[6] Meta-analysis was carried out for comparing HbA1c and weight results for 10 mg dapagliflozin versus placebo in the intermediate term (12 to 26 weeks) and longer term (48 to 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% confidence intervals (95% CI). Heterogeneity was assessed using the I^2 statistic. Where necessary, standard deviations were calculated from confidence intervals or standard errors 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.

Figure 1. Search results



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 weeks 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 3,398 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 (Bolinder 2012)[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 mg to 20 mg, used as once daily preparations. Doses of canagliflozin ranged from 50 mg 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]

Except for the study by Nauck 2011,[11] all studies included a placebo group. Two studies included an active comparator: glipizide (mean dose 16 mg) in the study by Nauck 2011,[11] and sitagliptin (100 mg) in the canagliflozin study.[16]

Most studies included lead in periods (median of two 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 quality of life 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 was 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 of 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.

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 2010[8] **Design:** multi-centre (n=80), 4-arm, double blind, placebo controlled RCT **Duration:** 24 weeks **Follow-up:** 102 weeks **Quality:** high	**N:** 534 **Age (years):** 54 to 55 SD9 to 10 **HbA1c (%):** 7.9 to 8.2 SD0.8 to 1.00 **BMI (kg/m^2):** 31.2 to 31.8 SD5.4 to 6.2	**Intervention:** 2.5, 5 or 10 mg dapagliflozin once daily **Comparator:** placebo **Background antidiabetic therapy:** metformin (≥1500 mg/day)	**HbA1c (%):** -0.54 (-0.74, -0.34) **Weight (kg):** -2.00 (-2.67, -1.33) **FPG (mmol/L):** -0.97 (95% CI NR) **SBP (mmHg):** -4.9 (95% CI NR)
Bolinder 2012[9;10] **Design:** multi-centre (n=40), 2-arm, double blind, placebo controlled RCT **Duration:** 24 weeks **Follow-up:** 78 week extension **Quality:** high	**N:** 180 **Age (years):** 61 SD7 to 8 **HbA1c (%):** 7.2 SD0.4 to 0.5 **BMI (kg/m^2):** 31.7 to 32.1 SD3.9	**Intervention:** 10 mg dapagliflozin once daily **Comparator:** placebo **Background antidiabetic therapy:** metformin (≥1500 mg/day)	**HbA1c (%):** -0.29 (-0.42, -0.16) **Weight (kg):** -2.08 (-2.84, -1.32) **FPG (mmol/L):** -0.95 (-1.33, -0.57) **SBP (mmHg):** -2.8 (-5.9, 0.2)
Nauck 2011[11] **Design:** multi-centre (n=95), 2-arm, double blind, active controlled RCT **Duration:** 52 weeks **Follow-up:** 156 week extension **Quality:** high	**N:** 801 **Age (years):** 58 to 59 SD9 to 10 **HbA1c (%):** 7.7 SD0.9 **BMI (kg/m^2):** 31.2 to 31.7 SD5.1	**Intervention:** dapagliflozin once daily (mean dose 9.2 mg) **Comparator:** glipizide (mean dose 16.4 mg) **Background antidiabetic therapy:** metformin (≥1500 mg/day)	**HbA1c (%):** 0.0 (-0.11, +0.11) **Weight (kg):** -4.66 (-5.15, -4.17) **FPG (mmol/L):** -0.20 (95% CI NR) **SBP (mmHg):** -5.1 (95% CI NR)
Rosenstock 2012[12] **Design:** multi-centre (n=105), 3-arm, double blind, placebo controlled RCT **Duration:** 24 weeks **Follow-up:** 24 week extension **Quality:** low	**N:** 420 **Age (years):** 53 to 54 SD10 to 11 **HbA1c (%):** 8.3 to 8.4 SD1.0 **BMI (kg/m^2):** 51 to 62% ≥30; 87 to 93% ≥25	**Intervention:** 5 or 10 mg dapagliflozin once daily **Comparator:** placebo **Background antidiabetic therapy:** pioglitazone (30 or 45 mg/day)	**HbA1c (%):** -0.55 (-0.71, -0.39) **Weight (kg):** -1.78 (-2.32, -1.24) **FPG (mmol/L):** -1.33 (95% CI NR) **SBP (mmHg):** -4.7 (95% CI NR)
Strojek 2011[13] **Design:** multi-centre (n=84), 4-arm, double blind, placebo controlled RCT **Duration:** 24 weeks **Follow-up:** 24 week extension **Quality:** high	**N:** 592 **Age (years):** 59 to 60 SD8 to 10 **HbA1c (%):** 8.1 SD0.7 to 0.8 **BMI (kg/m^2):** 45 to 51% ≥30; 80 to 86% ≥25	**Intervention:** 2.5, 5 or 10 mg dapagliflozin once daily **Comparator:** placebo **Background antidiabetic therapy:** glimepiride (4 mg)	**HbA1c (%):** -0.69 (-0.87, -0.51) **Weight (kg):** -1.54 (-1.88, -1.20) **FPG (mmol/L):** -1.47 (-1.86, -1.08) **SBP (mmHg):** -3.8 (-6.4, -1.2)

Study design	Participants	Interventions	Outcomes
Wilding 2009[14] **Design:** multi-centre (n=26), 3-arm, double blind, placebo controlled RCT **Duration:** 12 weeks **Follow-up:** 4 weeks **Quality:** medium	**N:** 71 **Age (years):** 56 to 58 SD7 to 11 **HbA1c (%):** 8.4 to 8.5 SD0.7 to 0.9 **BMI (kg/m^2):** 34.8 to 36.2 SD3.6 to 4.6	**Intervention:** 10 or 20 mg dapagliflozin once daily **Comparator:** placebo **Background antidiabetic therapy:** insulin (51 to 56 U) + OAD (≤79% metformin only, ≤25% metformin plus TZD, ≤12.5% TZD only)	**HbA1c (%):** -0.70 (-1.07, -0.33) **Weight (kg):** -2.60 (-3.94, -1.26) **FPG (mmol/L):** -0.86 (-2.13, +0.42) **SBP (mmHg):** NR
Wilding 2012[15] **Design:** multi-centre (n=126), 4-arm, double blind, placebo controlled RCT **Duration:** 24 weeks **Follow-up:** 24 + 56 week extension **Quality:** high	**N:** 800 **Age (years):** 59 to 60 SD8 to 9 **HbA1c (%):** 8.5 to 8.6 SD0.8 to 0.9 **BMI (kg/m^2):** 33.0 to 33.4 SD5.0 to 5.9	**Intervention:** 2.5, 5 or 10 mg dapagliflozin once daily **Comparator:** placebo **Background antidiabetic therapy:** insulin (77.1 U) ± OAD (~50% none, ~40% metformin only, rest combination)	**HbA1c (%):** -0.57 (-0.67, -0.40) **Weight (kg):** -2.04 (-2.57, -1.51) **FPG (mmol/L):** NR **SBP (mmHg):** -3.11 (-5.79, -0.43)
Canagliflozin			***Difference versus active / placebo (95% CI)***
Rosenstock 2012[16] **Design:** multi-centre (n=85), 7-arm, double blind, placebo and active controlled RCT **Duration:** 12 weeks **Follow-up:** 2 weeks **Quality:** medium	**N:** 451 **Age (years):** 52.9 SD8.1 **HbA1c (%):** 7.75 SD0.93 **BMI (kg/m^2):** 31.5 SD4.9	**Intervention:** 50, 100, 200 or 300 mg OD or 300 mg BD canagliflozin **Comparator 1:** placebo **Comparator 2:** 100 mg OD sitagliptin **Background antidiabetic therapy:** metformin (≥1500 mg)	**HbA1c (%):** -0.48 to -0.73 vs placebo; +0.04 to -0.21 vs sitagliptin (95% CI NR) **Weight (kg):** -1.2 to -2.3 vs placebo; -1.7 to -2.8 vs sitagliptin (95% CI NR) **FPG (mmol/L):** -1.1 to -1.7 vs placebo; -0.2 to -0.8 vs sitagliptin (95% CI NR) **SBP (mmHg):** +2.3 to -3.6 vs placebo; +1.8 to -4.1 vs sitagliptin (95% CI NR) [roughly proportional to dose, but no advantage of 300 mg BD vs OD]

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 2010[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 2012 / Ljunggren 2012[9;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 2011[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 2012[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 2011[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 2009[14]	Not reported	Not reported	Yes (single blind during lead in, double blind during study)	Yes – last observation carried forward	7.0%	Yes	Partially; matched for patient demographics, not for prior medications	Yes – 0.5% HbA1c difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Wilding 2012[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 2012[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

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 the Appendix.

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 weeks and for 48 to 52 weeks. Figure 3 shows the reductions in HbA1c in the seven study groups of the canagliflozin study (Rosenstock 2012)[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, -0.40, p<0.00001) after 12 to 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% (Bolinder 2012)[9]. The WMD in HbA1c for studies with a baseline HbA1c value of >7.5% was -0.59% (95% CI: -0.67, -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 to 52 weeks were similar to those at up to 26 weeks (three studies, WMD -0.54, 95% CI: -0.69, -0.38, p<0.00001).

In the study by Nauck 2011,[11] there was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by -0.52% (95% CI: -0.60, -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 the once daily and twice daily doses at 300 mg (-0.92% SE0.08 and -0.95% SE0.08 from baseline, Figure 3). The HbA1c reduction from baseline with sitagliptin was -0.74% SE0.08.

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

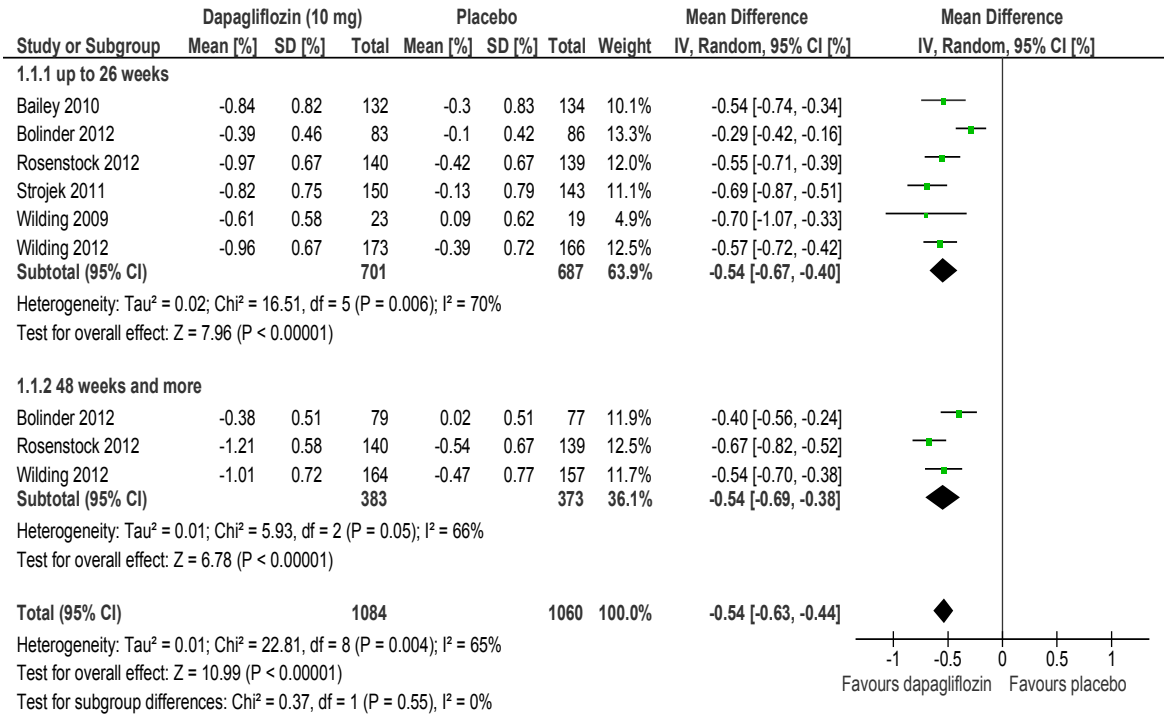
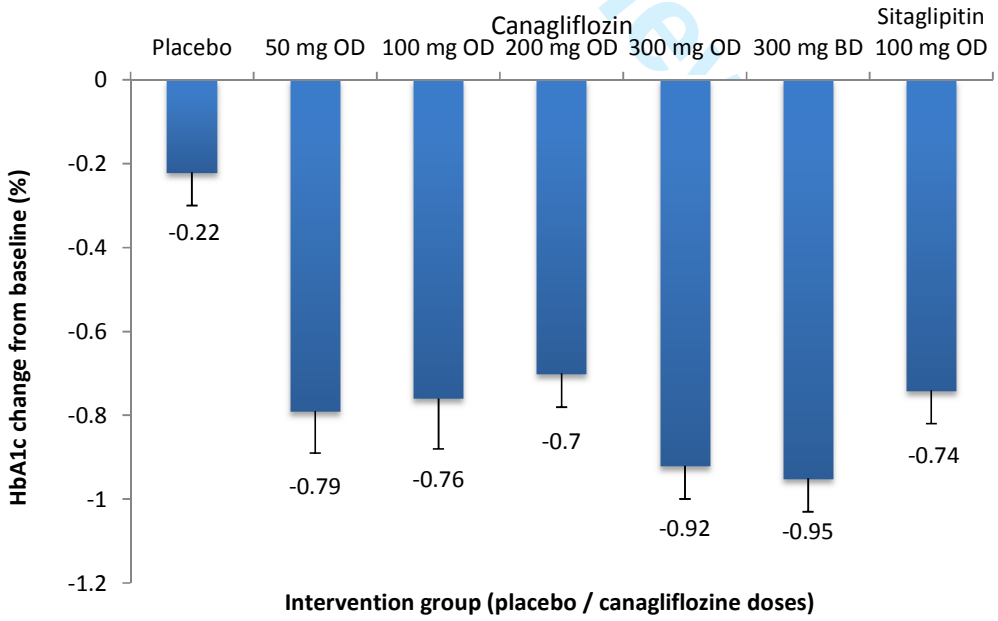


Figure 3. HbA1c change in response to canagliflozin (Rosenstock 2012, means and SE)



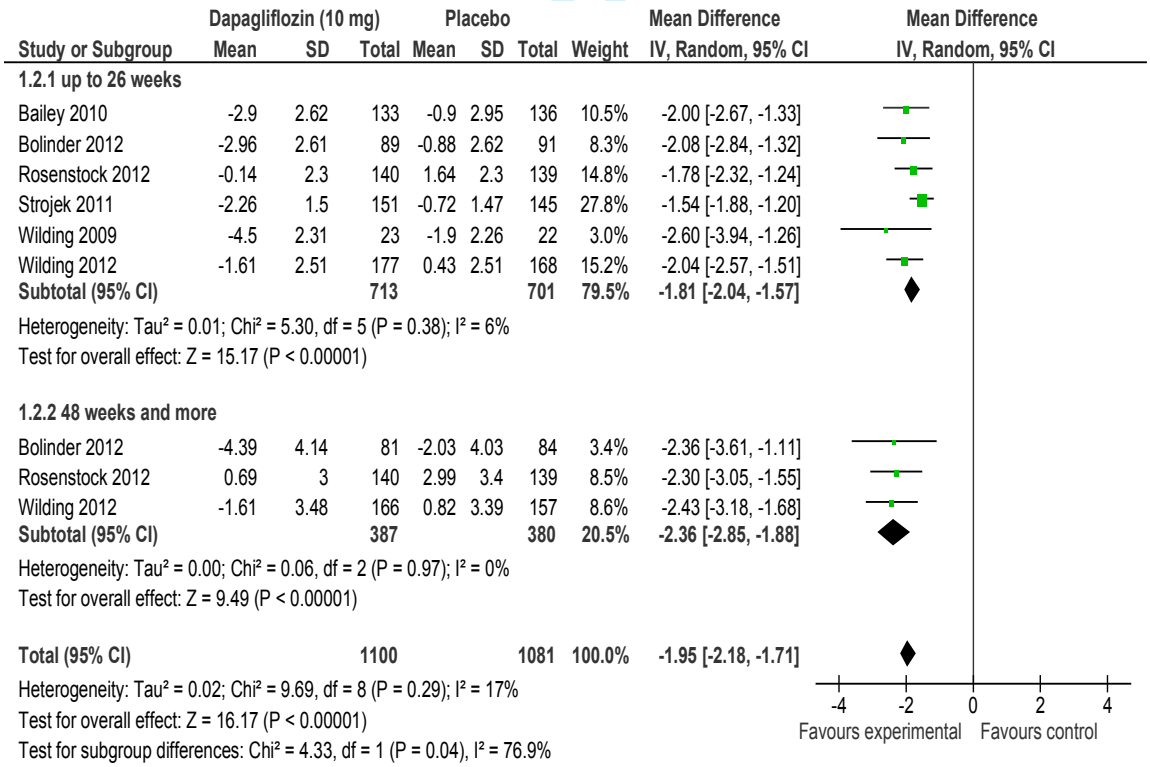
Weight

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 to 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, -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 to 52 weeks of treatment, weight was reduced by -2.36 kg (WMD, 95% CI: -2.85, -1.88, p<0.00001, three RCTs) compared to placebo (range +0.69 to -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, -2.87) in the dapagliflozin arm after 52 weeks of treatment and increased by +1.44 kg (95% CI: +1.09, +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 receiving 300 mg once and twice daily (versus -1.1 SE0.29 with placebo and -0.6 SE0.39 with sitagliptin).[16]

Wilding (2009) also recorded waist measurement, and reported reductions of 2.5 cm on dapagliflozin 10mg daily and 1.3 cm on placebo.

Figure 4. Meta-analysis for weight change from baseline, 10 mg dapagliflozin versus 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 mmHg in the 10 mg dapagliflozin groups compared to changes of +2.0 to -0.11 mmHg in the control groups. Rosenstock (2012) reported a systolic blood pressure reduction in response to canagliflozin ranging from -0.9 SE1.7 mmHg with 50 mg OD to -4.9 SE1.5 mmHg with 300 mg OD (-1.3 SE1.5 mmHg with placebo, -0.8 SE1.4 mmHg with sitagliptin).[16]

Fasting plasma glucose (FPG)

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 2011.[11]

Canagliflozin reduced FPG by between -0.9 and -1.4 mmol/L (SE0.20 to 0.22) with similar effects in the groups receiving 100, 200 or 300 mg OD or 300 mg BD (versus +0.2 SE0.20 mmol/L with placebo and -0.7 SE0.20 mmol/L with sitagliptin).[16]

Adverse events

Urinary and genital tract infection

Overall, there was a slight increase in the rate of urinary tract infections when comparing 10 mg dapagliflozin with placebo (risk ratio 1.44, 95% CI: 1.05, 1.98, p=0.02), with a mean rate of 8.8% in the 10 mg dapagliflozine group (range 0 to 12.1%) and of 6.1% in the control groups (range 0 to 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, 5.33, p<0.00001), with a mean rate of 9.5% in the 10 mg dapagliflozin groups (range 0 to 12.3%) and 2.6% in the control groups (range 0 to 5.2%).

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

In the canagliflozin study, rates of urinary tract infections 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% to 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, urinary 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 hypoglycaemia in the dapagliflozin groups ranged from 1.1% (Rosenstock 2012) to 56.6%. (Wilding 2012, any dose of dapagliflozin + insulin ± OAD).

Wilding 2009, 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 2011 reported a small, dose independent, increase in hypoglycaemia from dapagliflozin 2.5 mg, 5 mg 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 amongst 592 participants.[13] Nauck 2011 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 versus 162 events).[11]

Rosenstock 2012, comparing placebo to canagliflozin, found a hypoglycaemic event rate of 2% in the placebo group, of 0 to 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.[16]

Other adverse events

Three studies reported deaths in dapagliflozin groups (Bolinder 2011 (one death), Strojek 2011 (two deaths), Wilding 2012 (two deaths)).[9;13;15] 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 2011 in the glipizide group.[11]

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 versus 0% in Bolinder 2012, 9.1 versus 5.9% in Nauck 2011).[9;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 2011, rates were slightly higher in the dapagliflozin than in the glipizide group (5.9 versus 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 (2011) 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
- The sulphonylureas
- Pioglitazone
- Acarbose
- The meglitinide analogues, nateglinide and repaglinide
- The GLP-1 analogues
- The DPP-4 inhibitors
- The 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 co-morbidities
- Ease of use, by oral administration rather than injection
- Cost

The fear of hypoglycaemia can have a significant impact on the patient's quality of life. 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 two years. Del Prato and colleagues[18]), in an extension of the Nauck study with 624 of the original 801 participants, reported two year weight loss of 37kg on dapagliflozin compared to a gain of 1.36kg on glipizide. Wilding and colleagues[19]) in a follow-up of 64% of original participants, reported that by two years, weight had increased by 1.8kg in the placebo group but had decreased by 1.4kg in the 10mg 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 beta cell capacity.

Data of canagliflozin come from only one paper. Only two studies (Wilding 2009 and 2012) examined 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%. [21]

Musso et al. (2012)[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. is our focus on a real world use of SLGT2 inhibitors, and inclusion of recent trials. We excluded studies of less than eight weeks in duration, whilst Musso et al. analysed studies as short as two weeks. In addition, Musso et al. included studies with SGLT2 inhibitors are primary intervention, whilst 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, whilst also observing a reduction in serum uric acid and blood pressure. They concluded that there is an increased risk of urinary tract infections with SGLT2 inhibitors, with an odds ratio 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 amongst the controls was considered unexpected. An analysis by the manufacturers gave a standardised incidence ratio of 1.27 (95% CI: 0.58, 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 9 to 6 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.

Contributions

Rachel Court carried out literature searches. All authors helped design the data extraction form. Christine Clar and James Gill extracted data. Christine Clar, James Gill, and Norman Waugh drafted the article which has been approved by all authors.

Competing interests

None. CC, RC and NW work for Warwick Evidence, an independent academic health technology assessment group that supports the work of the UK National Institute for Health and Clinical Excellence.

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REFERENCES

(1) Diabetes UK. Diabetes in the UK: Key statistics on diabetes. http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf . 2010. Accessed: 2-8-2012.

(2) Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003; 289(1):76-79.

(3) Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB et al. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. The MILIS Study Group. *J Am Coll Cardiol* 1989; 14(1):49-57.

(4) Santer R, Kinner M, Lassen CL, Schneppenheim R, Eggert P, Bald M et al. Molecular analysis of the SGLT2 gene in patients with renal glucosuria. *J Am Soc Nephrol* 2003; 14(11):2873-2882.

(5) Hanefeld M, Forst T. Dapagliflozin, an SGLT2 inhibitor, for diabetes. *Lancet* 2010; 375(9733):2196-2198.

(6) Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. http://www.cochrane-handbook.org/. 2011. The Cochrane Collaboration. Accessed: 9-8-2012.

(7) WHO. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. WHO/NCD/NCS/99.2. 1999. http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf. Accessed: 9-8-2012.

(8) 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(9733):2223-2233.

(9) Bolinder J, Ljunggren O, Kullberg J, Johansson L, Wilding J, Langkilde AM et al. 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. *J Clin Endocrinol Metab* 2012; 97(3):1020-1031.

(10) Ljunggren O, Bolinder J, Johansson L, Wilding J, Langkilde AM, Sjostrom CD et al. 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 Obes Metab* 2012; 9999(9999).

(11) Nauck MA, Del PS, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care* 2011; 34(9):2015-2022.

(12) Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of Dapagliflozin, an SGLT2 Inhibitor, on HbA1c, Body Weight, and Hypoglycemia Risk in Patients With Type 2 Diabetes Inadequately Controlled on Pioglitazone Monotherapy. *Diabetes Care* 2012; 35(7):1473-1478.

(13) 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 Obes Metab* 2011; 13(10):928-938.

(14) Wilding JP, 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.

(15) Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med* 2012; 156(6):405-415.

(16) Rosenstock J, Aggarwal N, Polidori D, Zhao Y, 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.

(17) Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L et al. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. *Clin Pharmacol Ther* 2009; 85(5):520-526.

(18) Del Prato S, Nauck MA, Rohwedder K, Theuerkauf A, Langkilde AM, Parikh S. Long-term efficacy and safety of dapagliflozin vs add-on glipizide in patients with type 2 diabetes inadequately controlled with metformon: 2 year results. *47th Annual Meeting of Eureopan Association for the Study of Diabetes, Lisbon September 2011; S348*

(19) Wilding JP, Woo VC, Rohwedder K, Sugg JE, Parikh SJ. Long-term effectiveness of dapagliflozin over 104 weeks in patients with type 2 diabetes poorly controlled with insulin. *72nd Scientific Session of the American Diabetes Association June 2012: A267-268*

(20) Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, Philip S. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. *Health Tech Assessment 2010;14: no 36*

(21) Musso G, Gambino R, Cassader M, Pagano G. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. *Ann Med* 2012; 44(4):375-393.

(22) Food and Drug Administration. Summary minutes of the endocronologic and metabolic drugs advisory committee. 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM262990.pdf. Accessed: 9-8-2012.

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**				**Funding source:** Astra-Zeneca and

type 2 diabetes who have inadequate glycaemic control with metformin. Diabetes Care 2011; 34: 2015-2022[11]		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 **Duration of diabetes:** 5.07 SD5.05 years	**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 **Duration of diabetes:** 5.64 SD5.36 years	**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:** 5.75 SD6.44 years

	FPG (mmol/L): 8.92 SD2.61		**FPG (mmol/L):** 9.36 SD2.89		**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	

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]				**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 Inhibitor (2.5, 5, or 10 mg dapagliflozin)plus glimepiride versus placebo plus glimepiride**
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				
Study quality	High – see quality table for further information			
Study particulars	**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			
Participant criteria	**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			
Interventions	**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			
Participant baseline data	**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
	Age: 60.3 SD10.16 years **Sex:** 49% male **BMI:** 86.2% ≥25 kg/m^2; 45.5% ≥30	**Age:** 59.9 SD10.14 years **Sex:** 50% male **BMI:** 84.4% ≥25 kg/m^2; 48.1% ≥30 kg/m^2	**Age:** 60.2 SD 9.73 years **Sex:** 50% male **BMI:** 80.3% ≥25 kg/m^2; 51.4% ≥30 kg/m^2	**Age:** 58.9 SD 8.32 years **Sex:** 43.7% male **BMI:** 79.5% ≥25 kg/m^2; 45% ≥30 kg/m^2

	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		**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		**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		**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 **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		**Group 2 (n= 24):** 10 mg dapagliflozin + OAD + insulin **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		**Group 3 (n= 24):** 20 mg dapagliflozin + OAD + insulin **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 Pain in extremity n=1	

			Upper resp. tract Infection 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

	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
Participant baseline data	**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) **Sex (% male)**	53.3 SD7.8 48%	53.3 SD8.5 53%	51.7 SD8.0 56%	52.9 SD9.6 51%	52.3 SD6.9 56%	55.2 SD7.1 44%	51.7 SD8.1 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

Title: 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% (WMD, 95% CI -0.67, -0.40) compared to placebo, but there was no difference compared to glipizide. Canagliflozin reduced HbA1c slightly more than sitagliptin (up to -0.21% versus sitagliptin). Both dapagliflozin and canagliflozin led to weight loss (dapagliflozin WMD -1.81 kg (95% CI -2.04, -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 FDA 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.

INTRODUCTION

Type 2 diabetes is one of the most important and prevalent chronic diseases today, with in 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 (NICE), recommend that if lifestyle intervention is insufficient, the first line of drug treatment is metformin, followed by a sulphonylurea, or sometimes a glitazone, before commencing 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 anti-diabetic 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. 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 to 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, e.g. metformin plus SGLT2 versus metformin plus sulphonylurea, and in triple therapy, e.g. 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 control 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 quality of life 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 to 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, effect should not vary by duration of disease. Type 2 diabetes is often a progressive disease with diminishing beta cell capacity.

Interventions

Any use of SGLT2 inhibitors (dapagliflozin, 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 quality of life

- Cardiovascular events

Adverse effects, including hypoglycaemia, urinary tract infection (UTI)

Search methods for identification of studies

We searched the following sources:

- MEDLINE
- MEDLINE in-Process
- EMBASE
- The Cochrane Library, all sections
- NHS HTA
- Science Citation Index Expanded (SCI expanded)
- On-going Trials Registers:
- Clinical trials (www.clinicaltrials.gov)
- Current Control Trials (www.controlled-trials.com/)
- American Diabetes Association – Conference Abstracts
- EASD – 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. 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. SGLT-2 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 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

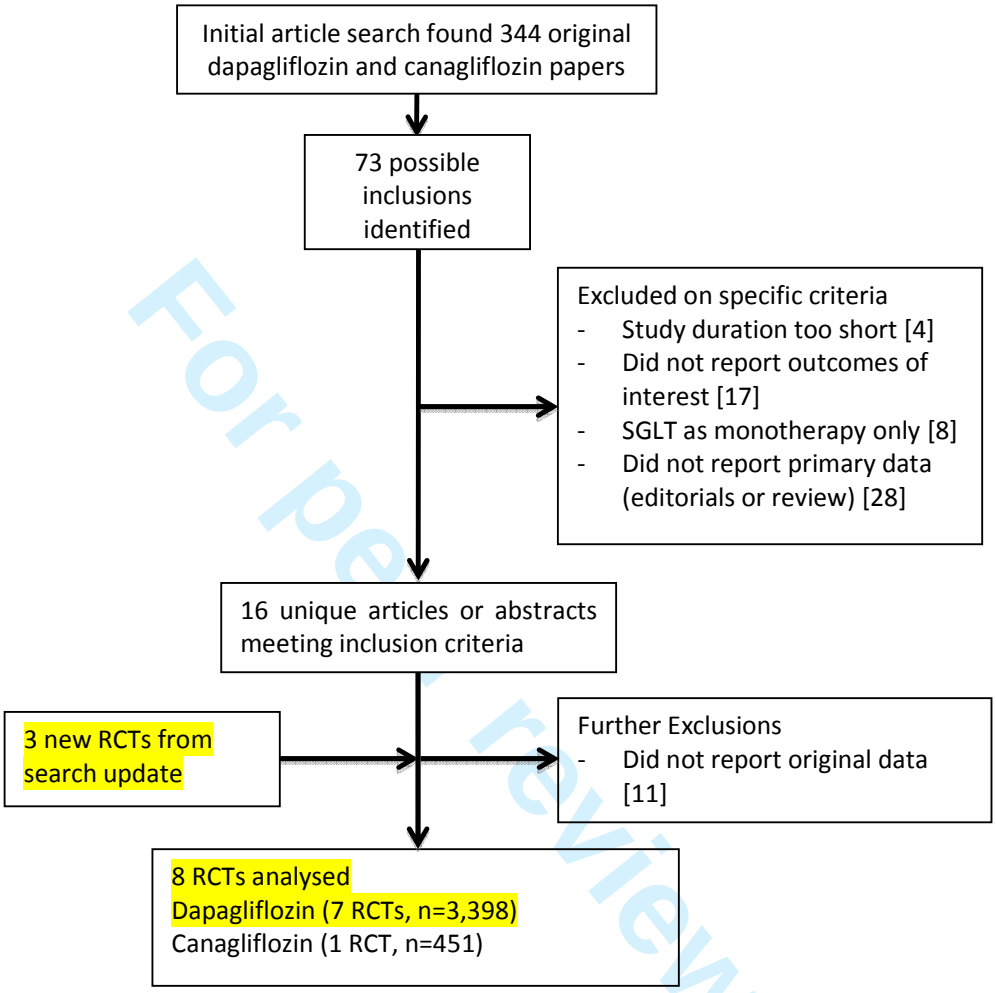
The data analysis has been reported according to the guide set down within the Cochrane Handbook for Systematic Reviews of Interventions.[6] Meta-analysis was carried out for comparing HbA1c and weight results for 10 mg dapagliflozin versus placebo in the intermediate term (12 to 26 weeks) and longer term (48 to 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% confidence intervals (95% CI). Heterogeneity was assessed using the I^2 statistic. Where necessary, standard deviations were calculated from confidence intervals or standard errors 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.

Figure 1. Search results



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 weeks 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 3,398 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 (Bolinder 2012)[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 mg to 20 mg, used as once daily preparations. Doses of canagliflozin ranged from 50 mg 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]

Except for the study by Nauck 2011,[11] all studies included a placebo group. Two studies included an active comparator: glipizide (mean dose 16 mg) in the study by Nauck 2011,[11] and sitagliptin (100 mg) in the canagliflozin study.[16]

Most studies included lead in periods (median of two 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 quality of life 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 was 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 of 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.

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 2010[8] **Design:** multi-centre (n=80), 4-arm, double blind, placebo controlled RCT **Duration:** 24 weeks **Follow-up:** 102 weeks **Quality:** high	**N:** 534 **Age (years):** 54 to 55 SD9 to 10 **HbA1c (%):** 7.9 to 8.2 SD0.8 to 1.00 **BMI (kg/m^2):** 31.2 to 31.8 SD5.4 to 6.2	**Intervention:** 2.5, 5 or 10 mg dapagliflozin once daily **Comparator:** placebo **Background antidiabetic therapy:** metformin (≥1500 mg/day)	**HbA1c (%):** -0.54 (-0.74, -0.34) **Weight (kg):** -2.00 (-2.67, -1.33) **FPG (mmol/L):** -0.97 (95% CI NR) **SBP (mmHg):** -4.9 (95% CI NR)
Bolinder 2012[9;10] **Design:** multi-centre (n=40), 2-arm, double blind, placebo controlled RCT **Duration:** 24 weeks **Follow-up:** 78 week extension **Quality:** high	**N:** 180 **Age (years):** 61 SD7 to 8 **HbA1c (%):** 7.2 SD0.4 to 0.5 **BMI (kg/m^2):** 31.7 to 32.1 SD3.9	**Intervention:** 10 mg dapagliflozin once daily **Comparator:** placebo **Background antidiabetic therapy:** metformin (≥1500 mg/day)	**HbA1c (%):** -0.29 (-0.42, -0.16) **Weight (kg):** -2.08 (-2.84, -1.32) **FPG (mmol/L):** -0.95 (-1.33, -0.57) **SBP (mmHg):** -2.8 (-5.9, 0.2)
Nauck 2011[11] **Design:** multi-centre (n=95), 2-arm, double blind, active controlled RCT **Duration:** 52 weeks **Follow-up:** 156 week extension **Quality:** high	**N:** 801 **Age (years):** 58 to 59 SD9 to 10 **HbA1c (%):** 7.7 SD0.9 **BMI (kg/m^2):** 31.2 to 31.7 SD5.1	**Intervention:** dapagliflozin once daily (mean dose 9.2 mg) **Comparator:** glipizide (mean dose 16.4 mg) **Background antidiabetic therapy:** metformin (≥1500 mg/day)	**HbA1c (%):** 0.0 (-0.11, +0.11) **Weight (kg):** -4.66 (-5.15, -4.17) **FPG (mmol/L):** -0.20 (95% CI NR) **SBP (mmHg):** -5.1 (95% CI NR)
Rosenstock 2012[12] **Design:** multi-centre (n=105), 3-arm, double blind, placebo controlled RCT **Duration:** 24 weeks **Follow-up:** 24 week extension **Quality:** low	**N:** 420 **Age (years):** 53 to 54 SD10 to 11 **HbA1c (%):** 8.3 to 8.4 SD1.0 **BMI (kg/m^2):** 51 to 62% ≥30; 87 to 93% ≥25	**Intervention:** 5 or 10 mg dapagliflozin once daily **Comparator:** placebo **Background antidiabetic therapy:** pioglitazone (30 or 45 mg/day)	**HbA1c (%):** -0.55 (-0.71, -0.39) **Weight (kg):** -1.78 (-2.32, -1.24) **FPG (mmol/L):** -1.33 (95% CI NR) **SBP (mmHg):** -4.7 (95% CI NR)
Strojek 2011[13] **Design:** multi-centre (n=84), 4-arm, double blind, placebo controlled RCT **Duration:** 24 weeks **Follow-up:** 24 week extension **Quality:** high	**N:** 592 **Age (years):** 59 to 60 SD8 to 10 **HbA1c (%):** 8.1 SD0.7 to 0.8 **BMI (kg/m^2):** 45 to 51% ≥30; 80 to 86% ≥25	**Intervention:** 2.5, 5 or 10 mg dapagliflozin once daily **Comparator:** placebo **Background antidiabetic therapy:** glimepiride (4 mg)	**HbA1c (%):** -0.69 (-0.87, -0.51) **Weight (kg):** -1.54 (-1.88, -1.20) **FPG (mmol/L):** -1.47 (-1.86, -1.08) **SBP (mmHg):** -3.8 (-6.4, -1.2)

Study design	Participants	Interventions	Outcomes
Wilding 2009[14] **Design:** multi-centre (n=26), 3-arm, double blind, placebo controlled RCT **Duration:** 12 weeks **Follow-up:** 4 weeks **Quality:** medium	**N:** 71 **Age (years):** 56 to 58 SD7 to 11 **HbA1c (%):** 8.4 to 8.5 SD0.7 to 0.9 **BMI (kg/m^2):** 34.8 to 36.2 SD3.6 to 4.6	**Intervention:** 10 or 20 mg dapagliflozin once daily **Comparator:** placebo **Background antidiabetic therapy:** insulin (51 to 56 U) + OAD (≤79% metformin only, ≤25% metformin plus TZD, ≤12.5% TZD only)	**HbA1c (%):** -0.70 (-1.07, -0.33) **Weight (kg):** -2.60 (-3.94, -1.26) **FPG (mmol/L):** -0.86 (-2.13, +0.42) **SBP (mmHg):** NR
Wilding 2012[15] **Design:** multi-centre (n=126), 4-arm, double blind, placebo controlled RCT **Duration:** 24 weeks **Follow-up:** 24 + 56 week extension **Quality:** high	**N:** 800 **Age (years):** 59 to 60 SD8 to 9 **HbA1c (%):** 8.5 to 8.6 SD0.8 to 0.9 **BMI (kg/m^2):** 33.0 to 33.4 SD5.0 to 5.9	**Intervention:** 2.5, 5 or 10 mg dapagliflozin once daily **Comparator:** placebo **Background antidiabetic therapy:** insulin (77.1 U) ± OAD (~50% none, ~40% metformin only, rest combination)	**HbA1c (%):** -0.57 (-0.67, -0.40) **Weight (kg):** -2.04 (-2.57, -1.51) **FPG (mmol/L):** NR **SBP (mmHg):** -3.11 (-5.79, -0.43)
Canagliflozin			***Difference versus active / placebo (95% CI)***
Rosenstock 2012[16] **Design:** multi-centre (n=85), 7-arm, double blind, placebo and active controlled RCT **Duration:** 12 weeks **Follow-up:** 2 weeks **Quality:** medium	**N:** 451 **Age (years):** 52.9 SD8.1 **HbA1c (%):** 7.75 SD0.93 **BMI (kg/m^2):** 31.5 SD4.9	**Intervention:** 50, 100, 200 or 300 mg OD or 300 mg BD canagliflozin **Comparator 1:** placebo **Comparator 2:** 100 mg OD sitagliptin **Background antidiabetic therapy:** metformin (≥1500 mg)	**HbA1c (%):** -0.48 to -0.73 vs placebo; +0.04 to -0.21 vs sitagliptin (95% CI NR) **Weight (kg):** -1.2 to -2.3 vs placebo; -1.7 to -2.8 vs sitagliptin (95% CI NR) **FPG (mmol/L):** -1.1 to -1.7 vs placebo; -0.2 to -0.8 vs sitagliptin (95% CI NR) **SBP (mmHg):** +2.3 to -3.6 vs placebo; +1.8 to -4.1 vs sitagliptin (95% CI NR) [roughly proportional to dose, but no advantage of 300 mg BD vs OD]

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 2010[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 2012 / Ljunggren 2012[9;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 2011[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 2012[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 2011[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 2009[14]	Not reported	Not reported	Yes (single blind during lead in, double blind during study)	Yes – last observation carried forward	7.0%	Yes	Partially; matched for patient demographics, not for prior medications	Yes – 0.5% HbA1c difference detectable	Astra-Zeneca and Bristol-Myers-Squibb
Wilding 2012[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 2012[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

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 the Appendix.

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 weeks and for 48 to 52 weeks. Figure 3 shows the reductions in HbA1c in the seven study groups of the canagliflozin study (Rosenstock 2012)[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, -0.40, p<0.00001) after 12 to 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% (Bolinder 2012)[9]. The WMD in HbA1c for studies with a baseline HbA1c value of >7.5% was -0.59% (95% CI: -0.67, -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 to 52 weeks were similar to those at up to 26 weeks (three studies, WMD -0.54, 95% CI: -0.69, -0.38, p<0.00001).

In the study by Nauck 2011,[11] there was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by -0.52% (95% CI: -0.60, -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 the once daily and twice daily doses at 300 mg (-0.92% SE0.08 and -0.95% SE0.08 from baseline, Figure 3). The HbA1c reduction from baseline with sitagliptin was -0.74% SE0.08.

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

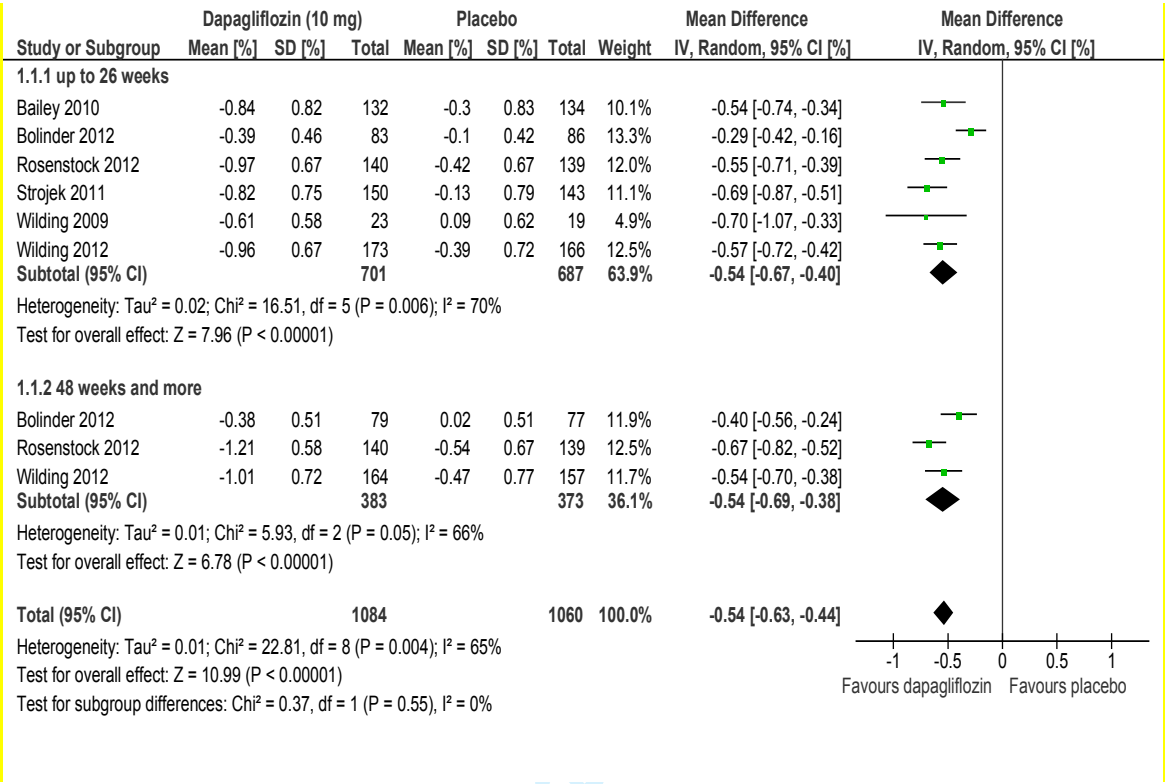
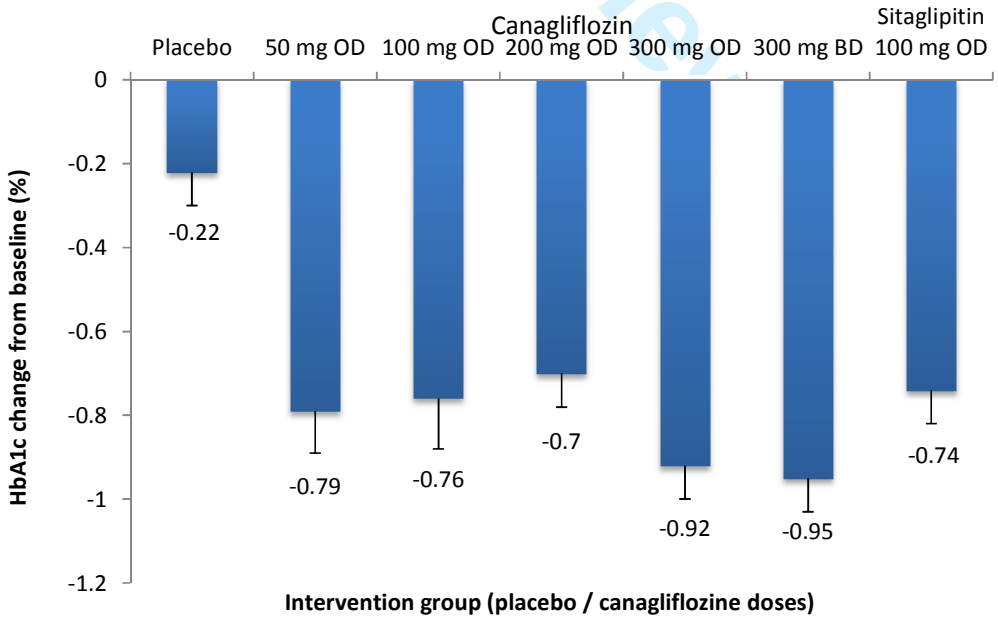


Figure 3. HbA1c change in response to canagliflozin (Rosenstock 2012, means and SE)



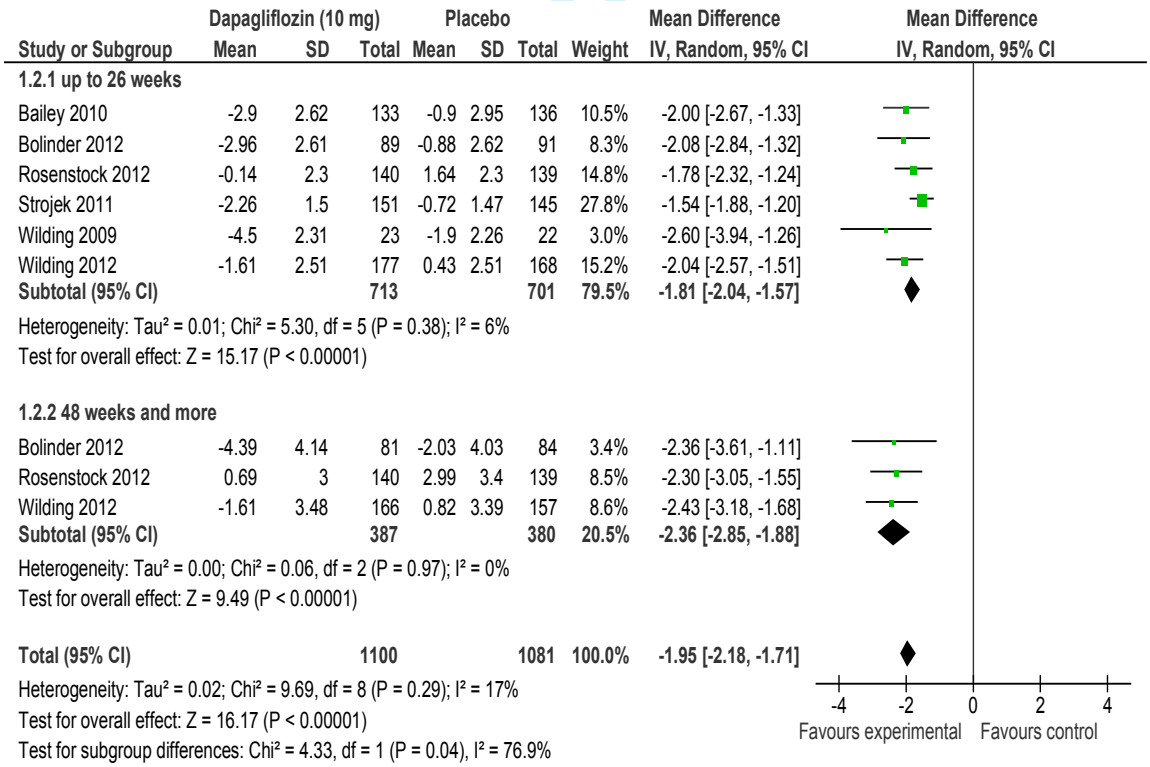
Weight

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 to 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, -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 to 52 weeks of treatment, weight was reduced by -2.36 kg (WMD, 95% CI: -2.85, -1.88, p<0.00001, three RCTs) compared to placebo (range +0.69 to -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, -2.87) in the dapagliflozin arm after 52 weeks of treatment and increased by +1.44 kg (95% CI: +1.09, +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 receiving 300 mg once and twice daily (versus -1.1 SE0.29 with placebo and -0.6 SE0.39 with sitagliptin).[16]

Wilding (2009) also recorded waist measurement, and reported reductions of 2.5 cm on dapagliflozin 10mg daily and 1.3 cm on placebo.

Figure 4. Meta-analysis for weight change from baseline, 10 mg dapagliflozin versus 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 mmHg in the 10 mg dapagliflozin groups compared to changes of +2.0 to -0.11 mmHg in the control groups. Rosenstock (2012) reported a systolic blood pressure reduction in response to canagliflozin ranging from -0.9 SE1.7 mmHg with 50 mg OD to -4.9 SE1.5 mmHg with 300 mg OD (-1.3 SE1.5 mmHg with placebo, -0.8 SE1.4 mmHg with sitagliptin).[16]

Fasting plasma glucose (FPG)

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 2011.[11]

Canagliflozin reduced FPG by between -0.9 and -1.4 mmol/L (SE0.20 to 0.22) with similar effects in the groups receiving 100, 200 or 300 mg OD or 300 mg BD (versus +0.2 SE0.20 mmol/L with placebo and -0.7 SE0.20 mmol/L with sitagliptin).[16]

Adverse events

Urinary and genital tract infection

Overall, there was a slight increase in the rate of urinary tract infections when comparing 10 mg dapagliflozin with placebo (risk ratio 1.44, 95% CI: 1.05, 1.98, p=0.02), with a mean rate of 8.8% in the 10 mg dapagliflozine group (range 0 to 12.1%) and of 6.1% in the control groups (range 0 to 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, 5.33, p<0.00001), with a mean rate of 9.5% in the 10 mg dapagliflozin groups (range 0 to 12.3%) and 2.6% in the control groups (range 0 to 5.2%).

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

In the canagliflozin study, rates of urinary tract infections 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% to 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, urinary 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 hypoglycaemia in the dapagliflozin groups ranged from 1.1% (Rosenstock 2012) to 56.6%. (Wilding 2012, any dose of dapagliflozin + insulin ± OAD).

Wilding 2009, 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 2011 reported a small, dose independent, increase in hypoglycaemia from dapagliflozin 2.5 mg, 5 mg 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 amongst 592 participants.[13] Nauck 2011 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 versus 162 events).[11]

Rosenstock 2012, comparing placebo to canagliflozin, found a hypoglycaemic event rate of 2% in the placebo group, of 0 to 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.[16]

Other adverse events

Three studies reported deaths in dapagliflozin groups (Bolinder 2011 (one death), Strojek 2011 (two deaths), Wilding 2012 (two deaths)).[9;13;15] 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 2011 in the glipizide group.[11]

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 versus 0% in Bolinder 2012, 9.1 versus 5.9% in Nauck 2011).[9;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 2011, rates were slightly higher in the dapagliflozin than in the glipizide group (5.9 versus 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 (2011) 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
- The sulphonylureas
- Pioglitazone
- Acarbose
- The meglitinide analogues, nateglinide and repaglinide
- The GLP-1 analogues
- The DPP-4 inhibitors
- The 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 co-morbidities
- Ease of use, by oral administration rather than injection
- Cost

The fear of hypoglycaemia can have a significant impact on the patient's quality of life. 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 two years. Del Prato and colleagues[18]), in an extension of the Nauck study with 624 of the original 801 participants, reported two year weight loss of 37kg on dapagliflozin compared to a gain of 1.36kg on glipizide. Wilding and colleagues[19]) in a follow-up of 64% of original participants, reported that by two years, weight had increased by 1.8kg in the placebo group but had decreased by 1.4kg in the 10mg 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 beta cell capacity.

Data of canagliflozin come from only one paper. Only two studies (Wilding 2009 and 2012) examined 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%. [21]

Musso et al. (2012)[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. is our focus on a real world use of SLGT2 inhibitors, and inclusion of recent trials. We excluded studies of less than eight weeks in duration, whilst Musso et al. analysed studies as short as two weeks. In addition, Musso et al. included studies with SGLT2 inhibitors are primary intervention, whilst 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, whilst also observing a reduction in serum uric acid and blood pressure. They concluded that there is an increased risk of urinary tract infections with SGLT2 inhibitors, with an odds ratio 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 amongst the controls was considered unexpected. An analysis by the manufacturers gave a standardised incidence ratio of 1.27 (95% CI: 0.58, 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 9 to 6 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.

Contributions

Rachel Court carried out literature searches. All authors helped design the data extraction form. Christine Clar and James Gill extracted data. Christine Clar, James Gill, and Norman Waugh drafted the article which has been approved by all authors.

Competing interests

None. CC, RC and NW work for Warwick Evidence, an independent academic health technology assessment group that supports the work of the UK National Institute for Health and Clinical Excellence.

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REFERENCES

(1) Diabetes UK. Diabetes in the UK: Key statistics on diabetes. http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf . 2010. Accessed: 2-8-2012.

(2) Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003; 289(1):76-79.

(3) Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB et al. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. The MILIS Study Group. *J Am Coll Cardiol* 1989; 14(1):49-57.

(4) Santer R, Kinner M, Lassen CL, Schneppenheim R, Eggert P, Bald M et al. Molecular analysis of the SGLT2 gene in patients with renal glucosuria. *J Am Soc Nephrol* 2003; 14(11):2873-2882.

(5) Hanefeld M, Forst T. Dapagliflozin, an SGLT2 inhibitor, for diabetes. *Lancet* 2010; 375(9733):2196-2198.

(6) Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. http://www.cochrane-handbook.org/. 2011. The Cochrane Collaboration. Accessed: 9-8-2012.

(7) WHO. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. WHO/NCD/NCS/99.2. 1999. http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf. Accessed: 9-8-2012.

(8) 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(9733):2223-2233.

(9) Bolinder J, Ljunggren O, Kullberg J, Johansson L, Wilding J, Langkilde AM et al. 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. *J Clin Endocrinol Metab* 2012; 97(3):1020-1031.

(10) Ljunggren O, Bolinder J, Johansson L, Wilding J, Langkilde AM, Sjostrom CD et al. 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 Obes Metab* 2012; 9999(9999).

(11) Nauck MA, Del PS, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care* 2011; 34(9):2015-2022.

(12) Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of Dapagliflozin, an SGLT2 Inhibitor, on HbA1c, Body Weight, and Hypoglycemia Risk in Patients With Type 2 Diabetes Inadequately Controlled on Pioglitazone Monotherapy. *Diabetes Care* 2012; 35(7):1473-1478.

(13) 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 Obes Metab* 2011; 13(10):928-938.

(14) Wilding JP, 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.

(15) Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med* 2012; 156(6):405-415.

(16) Rosenstock J, Aggarwal N, Polidori D, Zhao Y, 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.

(17) Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L et al. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. *Clin Pharmacol Ther* 2009; 85(5):520-526.

(18) Del Prato S, Nauck MA, Rohwedder K, Theuerkauf A, Langkilde AM, Parikh S. Long-term efficacy and safety of dapagliflozin vs add-on glipizide in patients with type 2 diabetes inadequately controlled with metformon: 2 year results. *47th Annual Meeting of Eureopan Association for the Study of Diabetes, Lisbon September 2011; S348*

(19) Wilding JP, Woo VC, Rohwedder K, Sugg JE, Parikh SJ. Long-term effectiveness of dapagliflozin over 104 weeks in patients with type 2 diabetes poorly controlled with insulin. *72nd Scientific Session of the American Diabetes Association June 2012: A267-268*

(20) Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, Philip S. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. *Health Tech Assessment 2010;14: no 36*

(21) Musso G, Gambino R, Cassader M, Pagano G. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. *Ann Med* 2012; 44(4):375-393.

(22) Food and Drug Administration. Summary minutes of the endocronologic and metabolic drugs advisory committee. 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM262990.pdf. Accessed: 9-8-2012.

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 **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		**Group 2 (start n= 91, analysed n= 89):** 10 mg dapagliflozin + metformin **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**				**Funding source:** Astra-Zeneca and

type 2 diabetes who have inadequate glycaemic control with metformin. Diabetes Care 2011; 34: 2015-2022[11]		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 **Duration of diabetes:** 5.07 SD5.05 years	**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 **Duration of diabetes:** 5.64 SD5.36 years	**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:** 5.75 SD6.44 years

	FPG (mmol/L): 8.92 SD2.61		**FPG (mmol/L):** 9.36 SD2.89		**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	

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]				**Funding source:** Astra-Zeneca and Bristol-Myers-Squibb **SGLT2 Inhibitor (2.5, 5, or 10 mg dapagliflozin)plus glimepiride versus placebo plus glimepiride**
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				
Study quality	High – see quality table for further information			
Study particulars	**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			
Participant criteria	**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			
Interventions	**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			
Participant baseline data	**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
	Age: 60.3 SD10.16 years **Sex:** 49% male **BMI:** 86.2% ≥25 kg/m^2; 45.5% ≥30	**Age:** 59.9 SD10.14 years **Sex:** 50% male **BMI:** 84.4% ≥25 kg/m^2; 48.1% ≥30 kg/m^2	**Age:** 60.2 SD 9.73 years **Sex:** 50% male **BMI:** 80.3% ≥25 kg/m^2; 51.4% ≥30 kg/m^2	**Age:** 58.9 SD 8.32 years **Sex:** 43.7% male **BMI:** 79.5% ≥25 kg/m^2; 45% ≥30 kg/m^2

	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		**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		**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		**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 **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		**Group 2 (n= 24):** 10 mg dapagliflozin + OAD + insulin **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		**Group 3 (n= 24):** 20 mg dapagliflozin + OAD + insulin **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 Pain in extremity n=1	

			Upper resp. tract Infection 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) **Sex (% male)**	53.3 SD7.8 48%	53.3 SD8.5 53%	51.7 SD8.0 56%	52.9 SD9.6 51%	52.3 SD6.9 56%	55.2 SD7.1 44%	51.7 SD8.1 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

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	no
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3 to 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	tables
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7

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Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	tables
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	tables
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Dapifloz peer review responses

Reviewer 1	
Written english is okay bit they did a ton of bullets that should be changed. Again, mentioned this in comments to authors.	
Major comments	
Overall comments: This is a systematic review discussing the SGTL2 receptor inhibitors used as combination therapy for treatment of type 2 diabetes. While this is an important topic as we need to know what is the best 2nd and 3rd line agent for type 2 diabetes, the article is limited in the lack of trials to include in this systematic review which make it tough to draw many conclusions regarding safety outcomes. In addition, only one of the studies is an active comparator while the rest are placebo controlled trials making the data less useful since we can't determine the comparisons between adding januvia versus an SGLT2 inhibitor for instance based on the data available. However, it does provide information on the general efficacy of SGLT2 inhibitors when used as combination therapy.	Fair points, but we can only report what research there is. And it is not correct that only one trial had an active comparator – there were two active comparators, glipizide in Nauck 2011 and sitagliptin in Rosenstock 2010.
1) The introduction needs to address why this topic needed a systematic review. i.e. Few people know about the potential benefits or harms of SGTL2 inhibitors used as dual or triple combination therapy for type 2 diabetes; therefore, we decided to conduct as systematic review of SGTL2 inhibitors to assess the efficacy and safety of these agents used as combination therapy for adults with type 2 diabetes. Would add safety not just efficacy into all statements where you say you are assessing efficacy since you do also	Section added at end of Introduction with similar message to referee's comments, and mentioning safety.

assess safety in your results.	
2) The appendix table is okay but is so big and long that it does not provide a great summary of the articles within one viewing segment. I would recommend another summary table showing key aspects of the study so that all 5 articles can be viewed on one page listing in columns: N of participants, dose of drug in each arm and names of drugs in each arm can be listed as rows under each study, mean baseline a1c, mean age, gender, key inclusion/exclusion criteria, country of study, study quality, and change in a1c between groups (which can be calculated) and whether statistically significant differences between groups or not.	A summary table with all the variables suggested by the referee would be rather large, but we take the point that a summary table would be useful. We have inserted one which is not quite as extensive as he suggested.
3) The discussion talks about the lack of long term data on safety and long term outcomes but does not mention the potential safety concerns of cancer, liver toxicity, and nephropathy. These were brought up in the FDA review of the drug and was why it was not yet FDA approved. I think it is reasonable to mention these issues to the reader and note that we need further studies specifically in these areas to address potential concerns of specific adverse effects.	We have added a paragraph on the FDA review.
4) I found the article results difficult to follow since there was no range in mean differences between groups. This could probably be helped by either putting that in the text or adding the summary table to the article as discussed in #2.	Table added
Minor issues	
1) Abstract background: consider adding at the end of the sentence “, and little is known regarding their efficacy and safety when used as dual or triple therapy for type 2 diabetes.” This will help make it	We have added some text to the Objective in the Abstract to make it clear that our review is about the use of these drugs in dual or triple therapy.

more clear to the reader why a systematic review needs to be conducted.	
2) Abstract objective: consider adding "and safety" after effectiveness. May want to change effectiveness to efficacy since data are all from RCTs which are mainly efficacy trials not effectiveness trials done in the "real world".	Safety added.
3) Abstract Inclusion criteria: consider adding randomized before the word trials.	We have added "randomised controlled"
4) Abstract Results: Seems like you could put the range in between group differences for a1c and weight loss for the placebo controlled trials here. Also, trial quality appeared good does not sound scientific. You used a validated instrument to assess risk of bias-why not provide the quantitative results of that assessment in results.	Figures for HbA1c changes added to Abstract. No change to "good quality" – it's a standard expression in systematic reviews. Text on safety added to Abstract.
5) Globally, I have never seen an article use so much bulleting before. One problem with bulleting is you feel a bit like you are reading an outline in some parts as opposed to a written article. Please fix that throughout unless the editor states differently. I would write it as a sentence with commas wherever this occurred.	We don't think the use of bullets is excessive but will amend it if the editor wishes.
6) I also found it hard to follow the headers since I am so used to articles being laid out in specific ways. (i.e. background, methods, results, and discussion). Usually, I only see subheadings under methods and results. I thought the subheadings in the background should be removed (i.e. subheading decision problem and review objectives – can keep text under subheadings just do not need the subheadings in my opinion – I found it	We have amended the structure slightly by having bolder headings for Introduction, Methods, Results, Discussion. We have removed the subheading on objectives, and the sentence that followed it, from the Introduction, and have expanded the preceding paragraph. However we have kept the subheadings in Methods and Results.

confusing), and under methods need to make less subheadings - could divide into 3 sections: data sources and selection (include search strategy, inclusion/exclusion criteria here), data extraction and quality assessment, and data synthesis and analysis.	
7) Would add rationale for systemative review as mentioned under major issues above prior to subheading listed as review objectives.	Done
8) Would consider removing the sentence under decision problem that states we start from the position that the first line drug in type 2 diabetes is metfromin… Although I agree that these meds are unlikely to replace metformin, you do not need the sentence since will state rationale for why you are looking at it in combination therapy. You could add a sentence earlier instead when talking about rationale for not looking at it in monotherapy by stating that a recent systematic review has already evaluated the class as monotherapy.	Paragraph removed – having expanded what is now the last paragraph of the Introduction, we no longer need the "Decision problem" section. Sentence added.
9) Above participants on page 3, delete the two sentences above participants which discuss outcomes and looking at trials against placebo since this should be and is under methods already. Redundent and does not need to be here.	We have removed the sentence on outcomes, since those appear in the Methods section. However since Questions 1 and 2 focus on active comparators, we think it is worth retaining the sentence on placebo trials. We have reduced the length of this section by amalgamating questions 1 and 2.
10) Would start methods before study participants and all the following information should be put without bullets under one of the three headings mentioned above.	Methods now starts as suggested. Subheadings retained
11) Would remove all times when you state "if data permitted". You are just describing methods here. In results, you can state that there were no data to answer a specific question.	Done

12) In methods when you describe looking at subgroups, would consider removing the categories of duration. Not needed really. Just use the statement that you already have regarding exploring duration of diabetes.	Categories retained because this was to address a specific hypothesis
13) Report methods for synthesis of evidence of clinical effectiveness. I would move this sentence to right above your discussion of data synthesis and add the words "to be described in detail below".	OK, done, and subheading removed.
14) Study selection: would add the words inclusion/exclusion before the word criteria for clarity.	OK, done
15) I could not tell if the quality assessment was done independently by 2 reviewers. The word verified should be changed if it was done independently as verified makes me think someone only looked over someone's else's answers in which case it would be a serial not an independent review.	Changed from "independently verified" to "checked".
16) Usually the Figure 1 has two boxes above the one listed there. One box shows all sources of data and N of titles reviewed (i.e. medline N=12000, handsearch N=29, embase N=13000 with an N excluded between title and abstract review. A second box listing N abstracts reviews would come above N full articles reviewed with an arrow to the side listing N of exclusions. Usually there are some reasons for exclusion listed between abstract and full article review boxes – would add that here if available. Would also remove fig 1 from box and have as a title. "Figure 1: Study flow diagram" or Figure 1: literature search results could be used for instance.	The sources of data are in the text. Title of figure amended and text below moved to start of Results.
17) Would move results header to above the	Results heading moved, but most subheadings

sentence on literature search results. Would remove subheaders of participants, interventions, leadin periods, and power. Would consider replacing with one heading called study characteristics and quality or could have study characteristics followed by quality then rest of headers as is. Power paragraph should go under a more global assessment of quality. You provide the quality table but only discuss power in the text. Would choose a few key issues such as allocation concealment and total dropout from the table to discuss in the text as one quality paragraph total.	retained.
18) Would change figure 2 header to change in a1c by dapagliflozin dose.	Done
19) If able, would be useful to have standard error bars in figures 2 through 5	Some figures removed
20) Under SBP, mention if compared to placebo here so it is obvious to the reader. Would make sure that is clear for all results.	Fair point. Text added to clarify.
21) It was not clear from the article that dapagliflozin reduces SBP based on 2 articles. In discussion, could say that it may also reduce SBP but need more data to further substantiate this or please make more evident why you think this is true. I did not feel that two RCTs with small differences in one of them was sufficient to say with certainty and unclear from results if the -2.7 was statistically significant.	All four dapagliflozin trials reported SBP reductions.
22) In discussion, you list SGLT2 inhibitors under nine classes. Are these available for use in Canada? If so, keep here. If not, may want to point out that the other 8 classes are available for use and that this class is not yet approved for use in all	Being based in the UK, we don't know what is available in Canada. All the other 8 classes are available in the UK, and dapagliflozin is expected to be submitted for licensing soon.

countries.	
23) Limitations – you state wilder noted one case of renail failure. Seems like that should also be listed under adverse events section under results.	Ok, moved to Adverse events section
24) Statement about wilder matching by demographics but could be biased by differences in prior med use seemed a bit strange. If this was an RCT, then shouldn't the background meds have been similar between groups? Was it not?	Fair point. Sentence deleted.
25) Usually I see ceiling of effectiveness written as ceiling effect but that is in the US. If the Canadian terms are different, then leave as is. If not, then would change to ceiling effect.	No change. There could be ceiling effects in adverse events too
26) In discussion, you state that UTIs were only mild infections not requiring treatment. May be worth adding a statement afterward that we need more studies with more people to have sufficient power to determine if there were differences in more serious UTIs requiring treatment.	OK, text revised and we have added the figures from Nauck, the largest study and calculated percentages and CIs.
27) In conclusions, you state that SGLT2 inhibitors appear safe as much as can be assessed via short term trials. I would probably take the safe part out here – you could comment on the hypoglycemia effect if you want. You could state that they are effective at reducing a1c and weight. I would add a sentence stating that we can not be sure of its impact on long term outcomes or safety until long term large studies are conducted assessing both long term outcomes and rare adverse events such as cancer, renal failure, and liver toxicity among others.	Safe bit removed and paragraph on FDA review added.
28) Abstract conclusion – would remove safe	Done.

from the sentence and would state effective at reducing a1c and weight in short term RCTs.	
Reviewer 2 Jennifer Hirst	
Presentation of results in the abstract is too brief and and needs to provide an answer to the research questions	Abstract is already close to word limit.
Text in search methods states that 344 hits were returned from searches whereas Figure 1, the Flow chart only begins with 73 articles. Nowhere in the text is this discrepancy clarified.	Figure 1 revised to clarify this
A description of the statistical methods needs to be given.	None used.
On page 6 details of study participants are presented, with numbers in brackets, it needs to be made clear whether these numbers represent the range or confidence intervals.	Clarified by addition of “range”
References for all the included studies should be included in the reference list.	Done
Written presentation: Page 6 - Lead in periods - wording in the last sentence is unclear: "Only in the Rosenstock..."	Revised
Page 8 Body Weight - the first sentence extends to 6 lines and needs breaking into at least 3 sentences.	Revised
Page 8 last sentence - not clear what the message is here.	That weight loss in trials may be due to being in the trial not due to the drugs.
Appendix. One of the studies in the table (Rosenstock) has no details of number of participants	The total number is given.
Appendix: pages 15 and 16 - Group 4 -10mg dapagliflozin - is this in combination with metformin? If not, then it does not meet the	Yes is in combination with metformin – added to box.

inclusion criteria.	
The results of this systematic review have been presented in graphical format, with data points from all included studies plotted together. In this format it is difficult to interpret the data, though the authors have attempted to do this through narrative and overall statements. The authors state that a meta-analysis was not conducted because of the small number and heterogeneity of the trials. As 5 trials have been included in the review, and each of these report outcomes which can be compared, a meta-analysis could be conducted. The authors throughout the paper make summary statements about the results, however the method of analysis used by the investigators is not appropriate to draw these conclusions. A meta-analysis should be conducted and would substantially improve the paper.	A meta-analysis would have been entirely inappropriate because of the heterogeneity of the studies. No – a meta-analysis should not be done. You can't combine a study of triple therapy with others of dual, or one of canaglifozin with some of dapagliflozin, or studies with different comparators.
A table summarising the study characteristics of included studies is needed in the results section. Suggest to include details of intervention & comparator medications, numbers of participants in each arm, dose and length of study.	Table added with the arms of most interest.
The curved line connecting the points on the graphs implies that the trend has been observed. As this is not the case, a straight line or preferably a dotted line would be more appropriate. In addition, confidence intervals should be provided on the graphs, with data points being slightly offset so confidence intervals can be seen.	Lines removed.
Results - 1st paragraph - in the text report SGLT2 inhibitors to lower HbA1c by between -0.52 and -0.78%, but Figure 2 shows this to be	Corrected.

between -0.37 and -0.78%	
-2nd paragraph - "no difference ... between dapagliflozin and glipizide" - Figure 2 appears to show a comparison of 2.5mg and 5mg. It is misleading to present data from an arm of the trial without dapagliflozin in this graph.	Accepted, and glipizide cross removed
There is no discussion of Figure 3 or Figure 5	Figure 3 now discussed. Figures 4 and 5 removed
Body weight - median weight reduction of -2.33kg presented with confidence intervals. Is this mean rather than median? How was this calculation perfomed and which statistical package was used to get to this value? This value should be obtained using meta-analysis.	Figures were as calculated in original studies. No meta-analysis should be done.
Significant reductions in weight, blood pressure and FPG reported without supporting statistics (means and confidence intervals).	
Hypoglycaemic - "a small but not significantly significant increase in ..... hypoglycaemia across 3 of the 4 studies" - The way the data is presented makes it difficult to judge whether hypoglycaemia is an issue. A meta-analysis of this data is needed to clarify this.	No change
Page 11 - 3rd paragraph. - "optimum dosage ...between 10-20mg" - of your 5 trials, there was only 1 trial which used a dose of over 10mg, and this was the smallest of the included trials with a maximum of 23 patients in each arm. No confidence intervals are presented, it is therefore not possible to say whether the observed difference at 20mg is significantly different from that at 10mg. There is insufficient evidence presented to conclude that an	Fair point, and paragraph replaced with new one.

optimum dosage of 10-20mg.	
The presentation of the results in this review needs to be revised. This could be achieved by conducting a meta-analysis. Data could then be presented in subgroups of dose. A summary statistic estimate need not be presented particularly if heterogeneity is large, but should be considered. The authors are strongly urged to conduct a meta-analysis of their data.	We remain convinced that a meta-analysis would not be appropriate.

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