

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

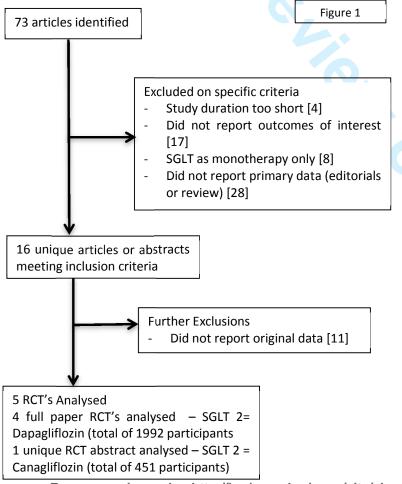
Study Selection: two reviewers using the defined criteria above selected studies independently. Any resulting discrepancies were resolved by discussion, with minimal third party mediation required.

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.



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  $32.7\text{kg/m}^2$  ( $31.2 - 36.27\text{kg/m}^2$ ) 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-

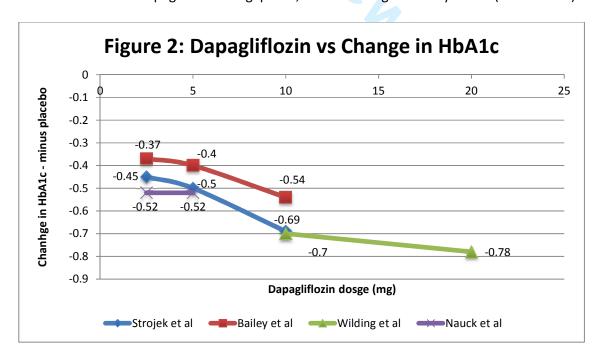
		Blinding and double dummy)	record carried forwards				0.35% difference detectable	Zeneca and Bristol- Myers- Squibb
Rosenstock 2010	Not reported	Yes (double blinding	Not reported	Not reported	Unclear	Yes	No comment on sample size calculation	Johnson and Johnson
Strojek 2011	Yes	Yes (Double Blinding and 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

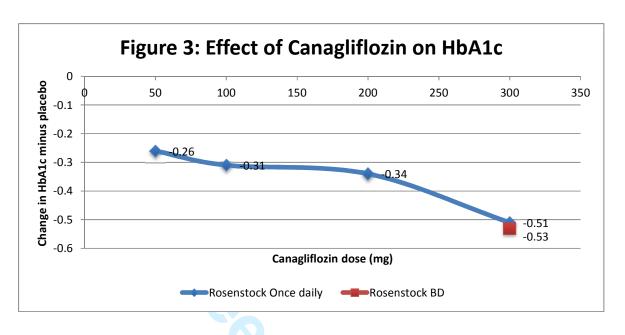
## **Results**

# **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)

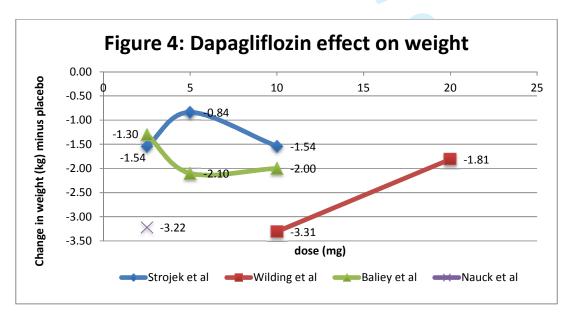
The SGLT2 inhibitors were shown, as demonstrated on Fig 2., to reduce HbA1c by between - 0.52 and -0.78% when adjusted for changes on placebo. There was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by 0.52% (Nauck 2011).





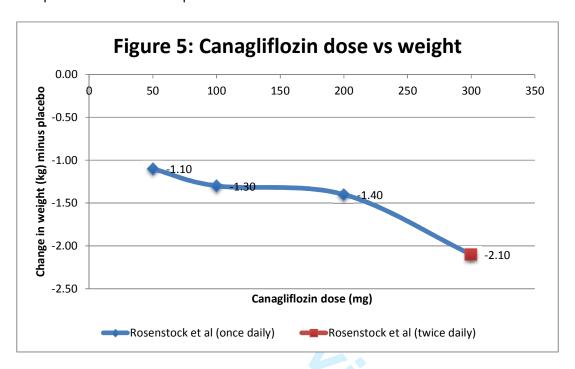
# **Body weight**

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 1<sup>st</sup> 2011)

- 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

- 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

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 20<sup>th</sup> 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 1<sup>st</sup> 2011)

 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 cotransport (SGLT) inhibitors. Systematic review and meta-analysis of randomised trials

Annals of Medicine, 2011, Early On-line 1-19



# Appendix

Effect of Dapag	s JL, Pieters A, Bastien A, List JF. Jliflozin in patients with type 2 diabetes who	have inadequate glycaemic control with	metformin: a randomised, double-blind,	Funding source: Astra-Zeneca and Bristol-Myers-Squibb							
<b>placebo-contro</b> Lancet 2010 (3	olled trial. 75):[2223-2233]			SGLT2 Inhibitor Vs. metformin							
Aim: Determin	e if dapagliflozin, lowers HbA1c in type 2 dial	petes in patients with inadequate HbA1c co	ntrol with metformin								
Study	Multi Centre: 81										
Particulars	Duration of intervention: 24 weeks										
	Duration of run in: 2 weeks										
	Followup: on completion of 24 weeks, a 10	22 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 222Proportion of patients achieving a therapeutic HbA1c, and										
	Glucose concentration,     ©©Total bodyweight										
	<ul> <li>No. with baseline HbA1c of 9% o</li> </ul>	r more. 222Change from baseline in	bodyweight, and decreases in bodyweight o	of 5% or more.							
Participant	N: 534 analysed										
Criteria	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										
	poorly controlled diabetes (including marked polyuria and polydipsia with >10% weight loss during the 3 months before enrolment); and systolic blood pressure 180 mm H										
	or more or diastolic blood pressure 110 mm Hg or more. Any significant other systemic disease										
	Lead in period: 2 weeks, single blind, to as	sess compliance with placebo, patients rar	ndomised successful completion. Metformi	n dose stabilised to >1500mg							
Quality	Study Quality: medium – See Quality table	for further information									
Participant	Group 1 (n analysed=134):	Group 2 (n= 135):	Group 3 (n= 133):	Group 4 (n= 132):							
paseline data	Placebo OD + metformin,	2.5mg dapagliflozin OD, metformin	5mg dapagliflozin OD, metformin	10mg dapagliflozin OD,							
	<b>Age:</b> 53.7 SD 10.3 years	<b>Age:</b> 55.0 SD 9.3 years	<b>Age:</b> 54.3 SD 9.4 years	<b>Age:</b> 52.7 SD 9.9 years							
	Sex: 55% Male	Sex: 51% Male	Sex: 50% Male	Sex: 57% male							
	<b>BMI (KG/M²):</b> 31.8 SD 5.3	<b>BMI (KG/M²):</b> 31.6 SD 4.8	<b>BMI (KG/M²):</b> 31.4 SD 5.0	BMI (KG/M <sup>2</sup> ): 31.2 SD 5.1							
	<b>HbA1c (%):</b> 8.11% SD 0.96	HbA1c (%): 8.96% SD 2.39	<b>HbA1c (%):</b> 8.17% SD 1.0	<b>HbA1c (%):</b> 7.92% SD 0.82							
	Duration of Diabetes: 5.8 SD 5.1	<b>Duration of Diabetes:</b> 6.0 SD 6.2	Duration of Diabetes: 6.4 SD 5.8	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) Systolic BP: 1		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 (chan	l ge from baseline	e at study end)						
,	nge from baseline at study end)  Group 1 (n analysed=134):  Placebo OD + metformin,		Group 2 (n= 1 2.5mg dapagl	135): liflozin OD, metformin	Group 3 (n= 133): 5mg dapagliflozin OD, metformin		Group 4 (n= 10mg dapag	
	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
		ycaemia = symptomatic episo very, capillary glucose <3.0mr	de, needing external assistance with mol/l)  Group 2 (n= 135):		UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoT = Hypotension HypoG = Hypoglycaemia Group 3 (n= 133):		Group 2 = n=89 Group 3 = n=95 Group 4 = n=98 Group 4 (n= 132):	
	Group 1 (n an	-						
	Placebo OD +	metformin,	2.5mg dapagl	liflozin OD, metformin	5mg dapaglifloz	in OD, metformin	10mg dapag	liflozin OD,
Specific	UTI: n= 11, GT	•	UTI: n= 6 GTI		UTI: n= 10, GTI n = 18		UTI: n= 16, GTI n =12,	
Events	HypoT n=1, Hy		HypoT n=0, H		HypoT n=2, Hyp	oG n=5,	HypoT n=0, I	<i>'</i> '
	Diarrhoea n= 7		Diarrhoea n=	-	Diarrhoea n= 5		Diarrhoea n=	<del></del>
	Back pain n= 7		Back pain n=		Back pain n= 3		Back pain n=	
	Nasopharyngi Cough n= 7	tis n= 11	Nasopharyng Cough n= 4	itis n= 12	Nasopharyngitis	5 n=4	Nasopharyng	gitis n= 8
	Influenza n= 1	Λ	Influenza n= 1	12	Cough n= 4 Influenza n= 13 Hypertension n= 4		Cough n= 1 Influenza n=	Q
	Hypertension		Hypertension	<del></del>			Hypertension	
	/ 1	act Infection n= 10	, , ,	ract Infection n= 5	, , ,	ct Infection n= 4		Tract Infection n= 3
	Headache n= 6		Headache n=		Headache n= 1	3CCO II- 4	Headache n=	
Safety Assessment		dverse events from the Medic				atient questionnaire and a		

	to S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al	Funding source: Astra-Zeneca and						
Diabetes care 2011	ipizide as Add-on Therapy in Patients with Type 2 diabetes who have inadequate glycaemic control w	ith Metformin Bristol-Myers-Squibb						
Diabetes care 2011	54.[2015-2022]	SGLT2 Inhibitor + metformin vs metformin + glipizide						
Aim: Compare effic	cacy, safety and tolerability of dapagliflozin with glipizide, in patients with type 2 diabetes poorly control	led 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	N: 801 analysed							
Criteria	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/							
	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							
		2 0 110010 p.101 to c.1110111118, 14011114 p.401114 B.40000 = 2201111101, 2						
	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI	; AST and/or ALT and/or creatine kinase ≥3 x upper limit of norm						
	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo	; AST and/or ALT and/or creatine kinase ≥3 x upper limit of norm						
Interventions	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI	; AST and/or ALT and/or creatine kinase ≥3 x upper limit of norm						
Interventions	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.	; AST and/or ALT and/or creatine kinase ≥3 x upper limit of norm						
Interventions	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin	; AST and/or ALT and/or creatine kinase ≥3 x upper limit of norm						
Interventions	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prior to randomization.	; AST and/or ALT and/or creatine kinase ≥3 x upper limit of norm H; systolic blood pressure ≥180mmHg and/or diastolic blood						
	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.  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	; AST and/or ALT and/or creatine kinase ≥3 x upper limit of norm H; systolic blood pressure ≥180mmHg and/or diastolic blood						
Quality	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.  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 Study Quality: medium – See Quality table for further information	l; AST and/or ALT and/or creatine kinase ≥3 x upper limit of norm H; systolic blood pressure ≥180mmHg and/or diastolic blood or glipizide 5mg. All patients maintained metformin						
Quality Participant	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.  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  Study Quality: medium − See Quality table for further information  Group 1 (start n= 406, analysed n=400):	t; AST and/or ALT and/or creatine kinase ≥3 x upper limit of normal; systolic blood pressure ≥180mmHg and/or diastolic blood  or glipizide 5mg. All patients maintained metformin  408, analysed n= 401):						
Quality	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.  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  Study Quality: medium − See Quality table for further information  Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin  Group 2 (start n= 5mg glipizide + metformin	l; AST and/or ALT and/or creatine kinase ≥3 x upper limit of norm H; systolic blood pressure ≥180mmHg and/or diastolic blood  or glipizide 5mg. All patients maintained metformin  408, analysed n= 401): etformin						
Quality Participant	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.  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  Study Quality: medium − See Quality table for further information  Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin  Age: 58 SD 9 years  Age: 59 SD 10 year	t; AST and/or ALT and/or creatine kinase ≥3 x upper limit of normal; systolic blood pressure ≥180mmHg and/or diastolic blood  or glipizide 5mg. All patients maintained metformin  408, analysed n= 401): etformin						
Quality Participant	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.  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  Study Quality: medium − See Quality table for further information  Group 1 (start n= 406, analysed n=400):  2.5mg dapagliflozin + metformin  Age: 58 SD 9 years  Age: 59 SD 10 years  Sex: 54.9§% Male	; AST and/or ALT and/or creatine kinase ≥3 x upper limit of normal; systolic blood pressure ≥180mmHg and/or diastolic						
Quality Participant	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.  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  Study Quality: medium − See Quality table for further information  Group 1 (start n= 406, analysed n=400):  2.5mg dapagliflozin + metformin  Age: 58 SD 9 years  Sex: 55.3% Male  BMI (KG/M²): 31.7 SD 5.1  BMI (KG/M²): 31.7 SD 5.1	t; AST and/or ALT and/or creatine kinase ≥3 x upper limit of normal; systolic blood pressure ≥180mmHg and/or diastolic blood  or glipizide 5mg. All patients maintained metformin  408, analysed n= 401): etformin ars 2 SD 5.1						
Quality Participant	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.  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  Study Quality: medium − See Quality table for further information  Group 1 (start n= 406, analysed n=400):  2.5mg dapagliflozin + metformin  Age: 58 SD 9 years  Age: 59 SD 10 years  Sex: 54.9§% Male	t; AST and/or ALT and/or creatine kinase ≥3 x upper limit of normal; systolic blood pressure ≥180mmHg and/or diastolic blood  or glipizide 5mg. All patients maintained metformin  408, analysed n= 401): etformin ars 2 SD 5.1						
Quality Participant	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.  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  Study Quality: medium − See Quality table for further information  Group 1 (start n= 406, analysed n=400):  2.5mg dapagliflozin + metformin  Age: 58 SD 9 years  Sex: 55.3% Male  BMI (KG/M²): 31.7 SD 5.1  BMI (KG/M²): 31.7 SD 5.1	t; AST and/or ALT and/or creatine kinase ≥3 x upper limit of normal; systolic blood pressure ≥180mmHg and/or diastolic blood  or glipizide 5mg. All patients maintained metformin  408, analysed n= 401): etformin ars 2 SD 5.1						
Quality Participant	Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmo total bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSI pressure ≥110 mmHg; significant other disease.  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  Study Quality: medium − See Quality table for further information  Group 1 (start n = 406, analysed n=400): 2.5mg dapagliflozin + metformin  Age: 58 SD 9 years  Sex: 55.3% Male  BMI (KG/M²): 31.7 SD 5.1  ≥ 25 kg/m²: 95%%  PM Model Sex: 54.9§% Male  BMI (KG/M²): 31.7 SD 5.1  ≥ 25 kg/m²: 90.75	; AST and/or ALT and/or creatine kinase ≥3 x upper limit of normal; systolic blood pressure ≥180mmHg and/or diastolic blood  or glipizide 5mg. All patients maintained metformin  408, analysed n= 401): etformin ars 2 SD 5.1 6						

	FPG (mmol/l): 9.0 SD 2.1		<b>FPG (mmol/l):</b> 9.1 SD 2.3	FPG (mmol/l): 9.1 SD 2.3			
Outcome (change	from baseline at study end)						
, , ,	<b>Group 1</b> (start n= 406, analysed n=40 2.5mg dapagliflozin + metformin	0):	<b>Group 2 (</b> 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	-	-	-	-			
		<u></u>		•			
Adverse Events	Minor hypoglycaemia (HypoM) = symptomatic episode, <3.5mmol/l)  Severe hypoglycaemia (HypoS) = symptomatic episode, assistance with following recovery, capillary glucose <3.0  Other hypoglycaemia (HypoO) = symptoms, but without confirming		rnal $\geq$ 3%				
	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= 26				
	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		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	, ·	Medical Dictionary or Regulatory Activti	es (MedDRA v12.1) via patient questionnaire	and active questioning during visits			

	Polidori D, Zhao Y, Sha S, Arbit D, Usiskin K et al.  an inhibitor of sodium glucose co-transporter 2, improves glycaemic control, lowers body weight, and improves beta cell function in	Funding source: Johnson and Johnson
subjects with	type 2 diabetes on background metformin	
Diabetologia 2	010 53:[S349]	Placebo + metformin
		VS
		SGLT2 Inhibitor + metformin OD
		Vs
		SGLT2 inhibitor BD + metformin OD
		Vs
		sitaglipitin OD + metformin
	ne safety, tolerability and efficacy of an alternative SGLT2 inhibitor Canagliflozin and remaining beta cell function, in DM type 2 patients whin as a monotherapy.	vho have inadequate glycaemic control
Study	Multi Centre: no comment in abstract	
Particulars	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 a	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	N: 451 analyzed against primary outcome	
Criteria		
	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	

A F2												
HA1c (%): 7.7%												
Duration of Diabetes: -												
FPG (mmol/l): 9.0												
ge from baseline	at study end)											
Group 1 placeb	o + metformin	Group 2 canagli	flozin 50mg +	Group 3 canaglifloz	in 100mg + metformin	Group 4 can	agliflozin 200mg +					
• •		Metformin	, and the second		· ·	metformin						
Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)					
-0.2	-	-0.45	-	-0.51	-	-0.54	-					
-	-	-1.3	-	-1.5	-	-1.6	-					
-	-	-0.9	-	-1.4	-	-1.8	-					
Mean	SD	Mean	SD	Mean	SD	Mean	SD					
-	-	-	-	-	-	-	-					
7.5	0.96	7.2	0.88	7.1	0.85	6.9	0.68					
Group 5 canagl	iflozin 300mg + metformin		flozin 300mg BD +	<b>Group 7</b> sitagliptin	+ metformin							
		metformin										
Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)							
-0.71	-	-0.73	-	-0.56	-							
-2.3	-	-2.3	-	+0.4	-							
-1.8	-	-1.7	-	-1.0	-							
Mean	SD	Mean	SD	Mean	SD							
-	-	-	-	-								
6.8	0.82	6.8	0.72	6.9	0.92							
At least one or	more adverse event balance	ed across all arms	save for:	<u> </u>								
Genital tract in	fections:	UTI		<b>Hypoglycaemia</b> (n	ot defined in							
3-8% canagliflo	zin arms	3-9% canagliflo	zin arms	abstract)								
2% placebo		6% placebo		0-6% canagliflozin arms								
2% sitagliptin		2% sitagliptin		2% placebo								
3	HA1c (%): 7.7% Duration of Dia FPG (mmol/l): 9 Systolic BP: -  ge from baseline Group 1 placeb  Mean -0.2 Mean - 7.5 Group 5 canagl  Mean -0.71 -2.3 -1.8  Mean - G.8  At least one or  Genital tract in 3-8% canagliflo	Sex: - BMI (KG/M²): 31.5 HA1c (%): 7.7% Duration of Diabetes: - FPG (mmol/l): 9.0 Systolic BP: -  ge from baseline at study end) Group 1 placebo + metformin  Mean  -0.2 Mean SD 7.5 0.96 Group 5 canagliflozin 300mg + metformin  Mean -0.71 -2.3 -1.8 Mean SD 6.8 0.82  At least one or more adverse event balance  Genital tract infections: 3-8% canagliflozin arms	Sex: -   BMI (KG/M²): 31.5     HA1c (%): 7.7%     Duration of Diabetes: -   FPG (mmol/l): 9.0     Systolic BP: -     Group 2 canagli     Metformin   Metformin   Metformin     Mean	Sex: -   BMI (KG/M²): 31.5   HA1c (%): 7.7%	Sex: - BMI (Kg/M²): 31.5     MAIc (%): 7.7%     Duration of Diabetes: - FPG (mmol/l): 9.0     Systolic BP: -	Sex   Sex	Sex:   BMI (KG/M²): 31.5   BMI (KG/M²): 31.					

	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.	Funding source: Astra-Zeneca and
	liflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-	Bristol-Myers-Squibb
blind, placebo-		2.5, 5, 10mg SGLT2 Inhibitor
Diabetes Obes.	Metab. 2011 13(10):[928-938]	(dapagliflozin) vs 4mg glimepiride
	ine efficacy, safety and tolerability of dapagliflozin treatment, as an add-on therapy to glimepiride, in patients with inadequately contro phonylurea monotherapy	olled type 2 diabetes who had been
Study	Multi Centre: 84 sites across 7 countries	
Particulars	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 <sup>2</sup>	
	FPG from baseline after 24weeks	
Participant	N: 592 analyzed	
Criteria		
	Inclusion criteria: Participants aged 18 years and older; inadequately controlled type 2 diabetes, BMI ≤45kg/m², HbA1c of ≥7 to ≤10.	
	least half maximum dose (max 4 mg) for at least 8 weeks prior to enrolment); fasting C-peptide ≥0.33 nmol/ml, fasting plasma glucos	se ≤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	on review for tho	ose 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 uptitration allowed; in case of inadequate glycaemic control, patients could receive open-label rescue therapy of metformin, pioglitazone or rosiglitazone; all patients receive dietary and lifestyle counseling and patients with BMI ≥27 kg/m² received advice regarding reducing caloric intake and increasing physical activity										
Quality		edium – See Quality table f			. a.i.g. caacii.g caici	io intane ana moreasm <sub>o</sub>	, pyo.ou. uoc.v.c	1			
Participant	Group 1 (n= 146)		Group 2 (n= 1		Group 3 (n= 145)		Group 4 (n= 151)				
baseline data	Placebo + glimepii	ride	• •	iflozin + glimepiride	5mg dapagliflozin	+ glimepiride	• •	iflozin + glimepiride			
	Age (years): 60.3	SD 10.16	Age (years): 59.9.3 SD 10.14		Age (years): 60.2 SD 9.73		Age (years): 58.9 SD 8.32				
	<b>Sex:</b> 49% male		Sex: 50% male		Sex: 50% male		<b>Sex:</b> 43.7% male				
	BMI (kg/m²)		BMI (kg/m²)		BMI (kg/m <sup>2</sup> )		BMI (kg/m²)				
	≥ 25 kg/m <sup>2</sup> : 86.2%	, D	≥ 25 kg/m <sup>2</sup> : 84.4%		≥ <b>25 kg/m²</b> : 78%		≥ <b>25 kg/m²</b> : 79.4%				
	≥ <b>30 kg/m²:</b> 45.5%	Ó	≥ 30 kg/m <sup>2</sup> : 4	8%	≥ <b>30 kg/m²</b> : 50%		≥ 30 kg/m <sup>2</sup> : 4	15.%			
	HbA1c (%): 8.15 S	D 0.74	<b>HbA1c (%):</b> 8.11, SD 0.75		HbA1c (%): 8.12 SD 0.78		<b>HbA1c (%):</b> 8.07 SD 0.79				
	Duration of diabe	tes (years): 7.4SD 5.7	<b>Duration of diabetes (years):</b> 7.7 SD		<b>Duration of diabetes (years):</b> 7.4 SD 5.7		<b>Duration of diabetes (years):</b> 7.2 SD 5.5				
	FPG (mmol/L): 9.5	58 SD 2.07	6.0		FPG (mmol/L): 9.68 SD 2.12		FPG (mmol/L): 9.55 SD 2.04				
	Systolic BP (mmHg): 133.3		<b>FPG (mmol/L):</b> 9.56, SD 2.13		Systolic BP (mmHg): 130.9		Systolic BP (mmHg): 133.8 SD 15				
			Systolic BP (m	mHg): 134.6							
Outcome (chan	ge from baseline at : Group 1 (n= 146)	study end)	Group 2 (n= 1	F.4\	Group 3 (n= 145)		Group 4 (n= 2	154)			
	Placebo + glimepi	rido	• •	iflozin + glimepiride	5mg dapagliflozin	+ alimonirido	•	iflozin + glimepiride			
	Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence	Mean	Confidence (95%)			
	iviean	Confidence (95%)	iviean	Confidence (95%)	ivieali	(95%)	ivicali	Confidence (95%)			
Δ from	-0.13	-	-0.58	-0.61 to -0.27	-0.63	-0.67 to -0.32	-0.82	-0.86 to -0.51			
baseline											
HbA1c (%)											
Δ from	-0.72	-	-1.18 -1.08 to +0		-1.56	-1.47 to -0.21	-2.26	-2.17 to -0.92			
baseline											
Weight (kg)											
Δ from	-0.33	-	-2.08	-2.50 to -1.00	-1.78	-2.20 to -0.68	-1.94	-2.34 to 0.87			
baseline FPG											
(mmol/L)											

Safety Assessment

	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Absolute Δ SBP from placebo	-1.20	-	-4.7	-6.1 to -0.9	-4.0	-5.5 to -0.2	-3.8	-6.4 to -1.2		
(mmHg)										
HbA1c	-	-	-	-	-	-	-	-		
			•	•			•			
Adverse Events	General events – where frequency is ≥3% in UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia		is 23% iii aiiy gi uup		<70mg/dl)	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	6)	Group 2 (n= 154)	Group 2 (n= 154)		Group 3 (n= 145)		Group 4 (n= 151)		
	Placebo + glime	piride	2.5mg dapagliflo	zin + glimepiride	5mg dapagliflozin + glimepiride		10mg dapagliflozin + glimepiride			
Specific Events	UTI: n=9, GTI n	= 1,	UTI: n=6, GTI n =	UTI: n=6, GTI n = 6,		UTI: n=10, GTI n = 9,		n = 10,		
	≥ 1Hypo n= 7		≥ 1Hypo n= 11		≥ 1Hypo n= 11	≥ 1Hypo n= 11		2		
	Bronchitis n= 4		Bronchitis n= 2		Diarrhoea n= 2	Diarrhoea n= 2		5		
	Diarrhoea n= 5		Diarrhoea n= 4	Diarrhoea n= 4			Diarrhoea n=	0		
	Back pain n= 4		Back pain n= 3		Nasopharyngiti	s n= 8	Back pain n=	7		
	Nasopharyngitis	s n= 4	Nasopharyngitis	n= 3	Arthralgia n= 0 Nasopharyngitis n=			itis n= 5		
	Arthralgia n= 4		Arthralgia n= 6		Upper resp. Tra	ct Infection n= 6	Arthralgia n= 1			

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

Hypertension n= 2

Upper resp. Tract Infection n= 5

Hypertension n= 8

Upper resp. Tract Infection n= 4

Hypertension n= 6

Upper resp. Tract Infection n= 4

Hypertension n= 2

	ood P, T'joen C, Bastien A, List JF, Fiedorek FT. Flozin in Patients With Type 2 Diabetes Receiving High Do	oses of Insulin Plus Insulin Sensitizers. Applicability of a novel in	Funding source: Astra-Zeneca and Bristol-Myers-Squibb				
independent treatr Diabetes care 2009			SGLT2 Inhibitor + patients own oral antidiabetic drugs (OAD) Vs insulin + OAD				
Aim: Determine if I	Dapagliflozin, lowers HBA1c in Type 2 diabetes in patients	with type 2 diabetes poorly controlled with high insulin doses p	olus 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%						
	<ul> <li>Percentage of end patients with final HbA1c</li> </ul>	<7%					
Participant	N: 65 analysed						
Criteria	Inclusion criteria: Participants aged between 18 years and 75; type 2 diabetes, BMI ≤45 kg/m², 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 exceeds						
	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 s						
	apper mines of normal, symptoms of severely						
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						
	dose adjustments to OADs; insulin could be down-titra						
	Lead in period: 10-21 day to establish reduced insulin dose						
Quality	<b>Study Quality:</b> Medium – See Quality table for further	information					
Participant	Group 1 (n analysed=19):		oup 3 (n= 23):				
baseline data	Placebo, OADs + insulin,	10mg dapagliflozin, OADs + insulin, 20m	ng dapagliflozin OD, OADs + insulin,				

	Age (years): 58.4 SD 6. Sex: 69.6% male BMI (kg/m²): 34.8 SD 4 HbA1c (%): 8.40% SD 0 Duration of diabetes (yef) FPG (mmol/L): 9.22 SD	4.6 0.9 <b>years):</b> 7.4SD 5.7	Age (years): 55.7 SD 9.2  Sex: 54.2% male  BMI (kg/m²): 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/m²): 36.2 SD 4.6 HbA1c (%):8.5% SD 0.9 Duration of diabetes (years): 11.3 SD 5.6		
	Systolic BP (mmHg): n,					FPG (mmol/L): 8.98 SD 3.06 Systolic BP (mmHg): n/a	
Outcome (change	from baseline at study en	id)					
	Group 1 (n analysed=19):		Group 2 (n= 23):		Group 3 (n= 23):		
	Placebo, OADs + insuli	in,	10mg dapagliflozin, OADs + insulin,		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,	General events – where frequency is >5%		At least one or more adverse event		
	capillary glucose <3.5m	nmol/L)	UTI = Urinary Tract Infection		<b>Group 1 =</b> n=15		
	Major hypoglycaemia	= symptomatic episode,	GTI = Genital Tract Infection		<b>Group 2 =</b> n=18		
	needing external assist	tance with following recovery,	HypoT = Hypotension		<b>Group 3 =</b> n=16		
	capillary glucose <3.0m	nmol/l)	HypoG = Hypoglycaemia		One patient in each group discontinued due to		
					adverse effects		
Specific Events	Group 1 (n analysed=1	19):	Group 2 (n= 23):		Group 3 (n= 23):		
	Placebo, OADs + insuli	in,	10mg dapagliflozin, OADs + insulin,		20mg dapagliflozin OD, OADs + insulin,		
	UTI: n=0, GTI n = 1,		UTI: n= 0, GTI n = 0,		UTI: n= 1, GTI n = 5,		
	HypoT n=n/a, HypoG n	ı=3	HypoT n=n/a, HypoG n=7,		HypoT n=n/a, HypoG n=6		
	Nausea n= 1		Nausea n= 1		Nausea n= 3		
	Pollakiuria n= 4		Pollakiuria n= 2		pollakiuria n= 3		
	Back pain n= 2		Back pain n= 3		vomiting n=3		
	Nasopharyngitis n= 2		Nasopharyngitis n= 2		Vulvovaginal mycotic infection n=3		
	Abdominal pain n= 2		Fatigue n= 2		Anxiety n=2		
	Influenza n= 2		Influenza n= 1		Back pain n= 2		
	Pain in extremity n= 1		Pain in extremity n= 2		Dry Mouth n=2		
	Upper resp. Tract Infec	ction n= 2	Upper resp. Tract Infection n= 2		Nasopharyngitis n=2		
	Headache n= 2		Headache n= 3		Peripheral odema n=2		
	Procedural pain n=2		Pharyngolaryngeal pain n=2		Abdominal pain n=2		
					Fatigue n= 1		
					Influenza n= 1		
					Pain in extremity		
					Upper resp. Tract	Infection n= 1	

Safety Assessment





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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			
2 Structured summary 3 4	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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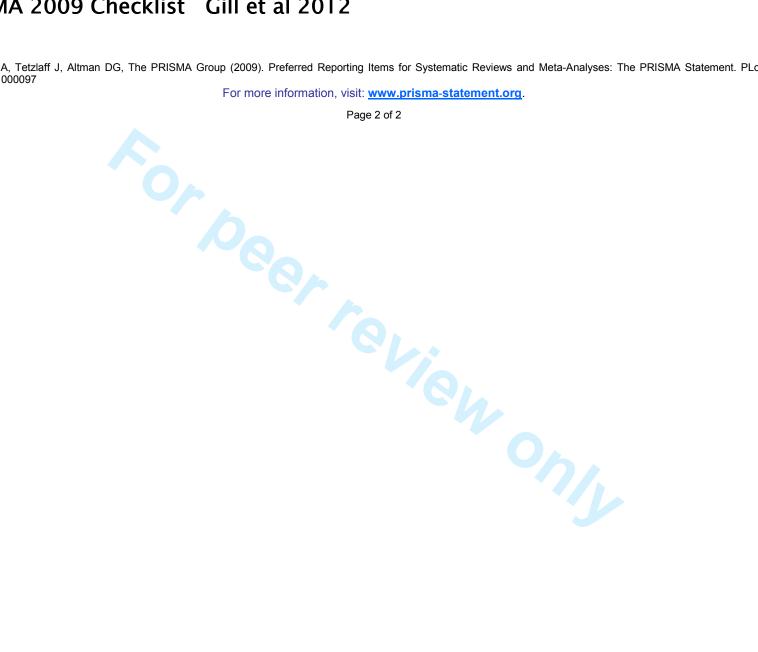
Synthesis of results  14 Describe the methods of handling data and com (e.g., I²) for each meta-analysis.	results of studies, if done, including measures of consistency N/A
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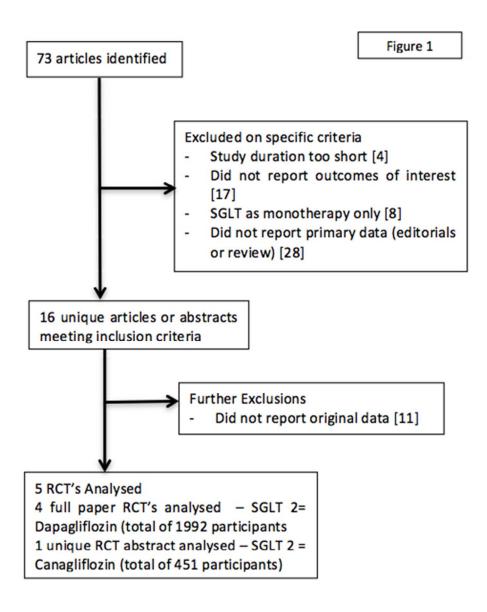
o 7 <u> </u>	Page 1 of 2				
Section/t	opic	#	Checklist item	Reported on page #	
11 Risk of bia	s across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A	
13 14 Additional 15	analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A	
RESULT	3				
18 Study sele	ction	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	
20 Study chai 21	acteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	tables	
23 Risk of bia	s within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6	
<sup>24</sup> 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	
27 Synthesis	of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a	
<sup>28</sup> Risk of bia	s across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6	
30 Additional	analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a	
31 32 DISCUSSION					
3 <sup>3</sup> Summary 34	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	
36 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	
38 Conclusior	ns	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12	
<sup>10</sup> FUNDING					
42 Funding 43		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





Results of literature search, and exclusions at each stage

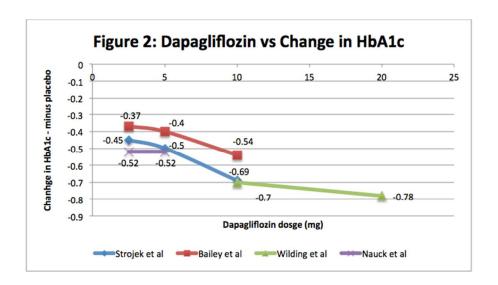
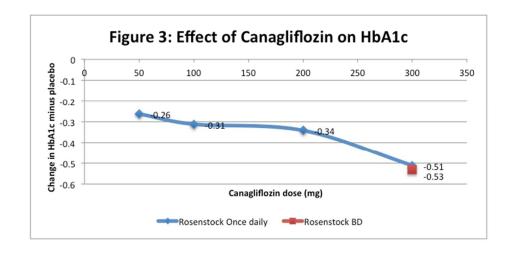
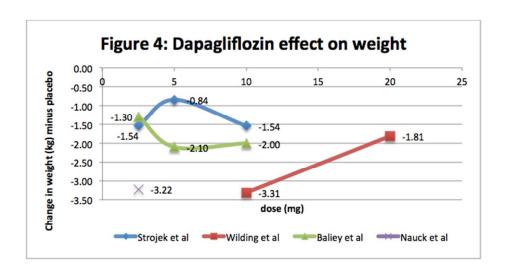


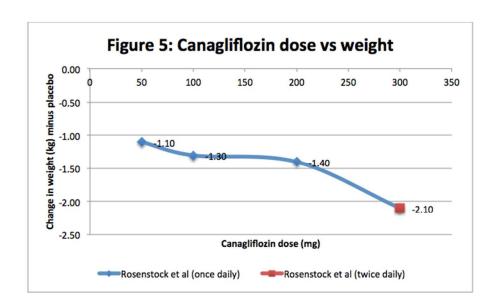
Figure showing reduction in HbA1c due to Dapagliflozin,



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	
<b>Primary Subject Heading</b> :	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	

SCHOLARONE™ Manuscripts



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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
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Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7



## PRISMA 2009 Checklist Gill et al 2012

Page 1 of 2			
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).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION	<u> </u>		
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
S 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



## 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	Fair points, but we can only report what research
discussing the SGTL2	there is.
receptor inhibitors used as combination therapy	And it is not correct that only one trial had an
for treatment of type	active comparator – there were two active
2 diabetes. While this is an important topic as we	comparators, glipizide in Nauck 2011 and
need to know what	sitagliptin in Rosenstock 2010.
is the best 2nd and 3rd line agent for type 2	Stagnpen in Noscristock 2010.
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.	
1) The introduction needs to address why this	Section added at end of Introduction with
topic needed a	similar message to referee's comments, and
systematic review. i.e. Few people know about	mentioning safety.
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	
critically stitle you do also	

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	Figures for HbA1c changes added to Abstract.  No change to "good quality" – it's a standard expression in systematic reviews.
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.	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.

	<u> </u>
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	Paragraph removed – having expanded what is now the last paragraph of the Introduction, we no longer need the "Decision problem" section.
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.	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

really. Just use the statement that you already have regarding exploring duration of diabetes.	
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
· · ·	Changed from "independently verified" to "checked".
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.  Results heading moved, but most subheadings

sentence on literature	retained.
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.	
10) Would shape figure 2 has been a	Done
18) Would change figure 2 header to change in	Done
a1c by dapagliflozin dose.	
19) If able, would be useful to have standard	Some figures removed
· · · · · · · · · · · · · · · · · · ·	Some figures removed
error bars in figures 2 through 5	
20) Hader CDD mention if commerced to allocable	Chin point Tout added to playify
20) Under SBP, mention if compared to placebo	Fair point. Text added to clarify.
here so it is obvious to	
the reader. Would make sure that is clear for all	
results.	
21) It was not along from the outide that	All four days slifter in twists you art of CDD
21) It was not clear from the article that	All four dapagliflozin trials reported SBP
dapagliflozin reduces SBP	reductions.
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.	
22) In discussion, you list SGLT2 inhibitors under	Being based in the UK, we don't know what is
nine classes. Are	available in Canada. All the other 8 classes are
these available for use in Canada? If so, keep	available in the UK, and dapagliflozin is expected
here. If not, may want	to be submitted for licensing soon.
to point out that the other 8 classes are available	
for use and that	
this class is not yet approved for use in all	
tino ciaso io not yet approved for use in all	

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.	
in short term NC13.	
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	A meta-analysis would have been entirely inappropriate because of the heterogeneity of the studies.
not appropriate to draw these conclusions. A meta-analysis should be conducted and would substantially improve the paper.	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	Figures were as calculated in original studies.  No meta-analysis should be done.
this value? This value should be obtained using meta-analysis.	·
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 dosagebetween 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.

We remain convinced that a meta-analysis would not be appropriate.
L

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

**Authors** 

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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.

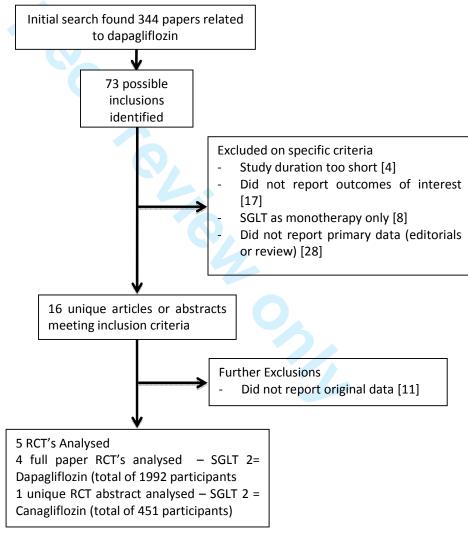
## Data synthesis and analysis

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

## **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<sup>2</sup> (range 31.2 – 36.27kg/m<sup>2</sup>) 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.

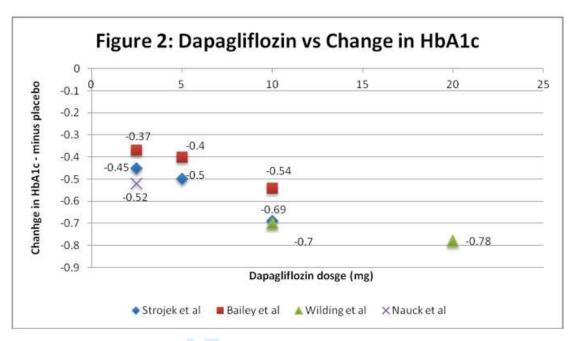
**Table 2: Study Quality** 

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

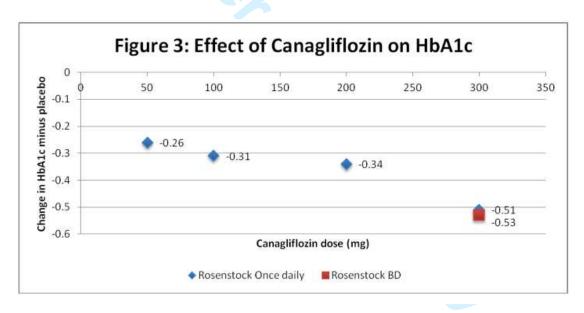
#### **HbA1c Levels**

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 1<sup>st</sup> 2011)

- 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 1<sup>st</sup> 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 20<sup>th</sup> 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 cotransport (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**

Effect of Dapag	JL, Pieters A, Bastien A, List JF. Sliflozin in patients with type 2 diabetes who	Funding source: Astra-Zeneca and Bristol-Myers-Squibb							
placebo-contro Lancet 2010 (3	75):[2223-2233]			SGLT2 Inhibitor Vs. metformin					
Aim: Determin	e if dapagliflozin, lowers HbA1c in type 2 dial	petes in patients with inadequate HbA1c co	ontrol with metformin						
Study	Multi Centre: 81								
Particulars	Duration of intervention: 24 weeks								
	Duration of run in: 2 weeks								
	Follow-up: on completion of 24 weeks, a 1	02 week long-term study							
	Design: 4-arm RCT, double blind, placebo	ontrolled							
	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:								
	<ul> <li>Fasting plasma</li> <li>Proportion of patients achieving a therapeutic HbA1c, and</li> </ul>								
	Glucose concentration     Total bodyweight								
	<ul> <li>No. with baseline HbA1c of 9% o</li> </ul>	r more. • Change from baseline in	bodyweight, and decreases in bodyweight	of 5% or more.					
Participant	N: 534 analysed								
Criteria	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								
	poorly controlled diabetes (including marked polyuria and polydipsia with >10% weight loss during the 3 months before enrolment); and systolic blood pressure 180 mm F								
	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	Group 1 (n analysed=134):	Group 2 (n= 135):	Group 3 (n= 133):	Group 4 (n= 132):					
baseline data	Placebo OD + metformin,	2.5mg dapagliflozin OD, metformin	5mg dapagliflozin OD, metformin	10mg dapagliflozin OD, metformin					
	<b>Age:</b> 53.7 SD 10.3 years	<b>Age:</b> 55.0 SD 9.3 years	<b>Age:</b> 54.3 SD 9.4 years	<b>Age:</b> 52.7 SD 9.9 years					
	Sex: 55% Male	Sex: 51% Male	Sex: 50% Male	Sex: 57% male					
	<b>BMI (KG/M<sup>2</sup>):</b> 31.8 SD 5.3	<b>BMI (KG/M²):</b> 31.6 SD 4.8	<b>BMI (KG/M<sup>2</sup>):</b> 31.4 SD 5.0	BMI (KG/M <sup>2</sup> ): 31.2 SD 5.1					
	<b>HbA1c (%):</b> 8.11% SD 0.96	HbA1c (%): 8.96% SD 2.39  Duration of Diabetes: 6.0 SD 6.2	HbA1c (%): 8.17% SD 1.0  Duration of Diabetes: 6.4 SD 5.8	<b>HbA1c (%):</b> 7.92% SD 0.82					
	Duration of Diabetes: 5.8 SD 5.1	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		<b>FPG (mmol/l):</b> 8.66 SD 2.15 <b>Systolic BP:</b> 126.0 SD 15.9	
Outcome (chan	l ige from baseline	e at study end)			ı			
•	Group 1 (n ana Placebo OD + i	lysed=134):	Group 2 (n= 13! 2.5mg dapaglifle	5): ozin 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
		ycaemia = symptomatic episo overy, capillary glucose <3.0mr	de, needing external assistance with mol/I)		UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoT = Hypotension HypoG = Hypoglycaemia		<b>Group 2 =</b> n=89 <b>Group 3 =</b> n=95 <b>Group 4 =</b> n=98	
	Group 1 (n and Placebo OD +	-	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, GT HypoT n=1, Hy	/poG 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 Nasopharyngi	7	Diarrhoea n= 3 Back pain n= 5 Nasopharyngitis	s n= 12	Diarrhoea n= 5 Back pain n= 3 Nasopharyngitis n=4		Diarrhoea n= Back pain n= Nasopharyng	10
	Cough n= 7 Influenza n= 1	0	Cough n= 4 Influenza n= 13		Cough n= 4 Influenza n= 13		Cough n= 1 Influenza n=	8
	Hypertension n= 6 Upper resp. Tract Infection n= 10 Headache n= 6		Hypertension n= 9 Upper resp. Tract Infection n= 5 Headache n= 4		Hypertension n= 4 Upper resp. Tract Infection n= 4 Headache n= 1		Hypertension n= 5 Upper resp. Tract Infection n= 3 Headache n= 11	
Safety Assessment		dverse events from the Medic		egulatory Activities (Me		atient questionnaire and		

	to S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al  ipizide as Add-on Therapy in Patients with Type 2 diabetes who have  24:12015-20221	ve inadequate glycaemic control with Metformin	Funding source: Astra-Zeneca and Bristol-Myers-Squibb					
Diabetes care 2011	. 54.[2015-2022]		SGLT2 Inhibitor + metformin vs metformin + glipizide					
Aim: Compare effic	acy, 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 stud	dy						
	Design: 2-arm parallel group, RCT.							
	Primary outcome: Absolute change from baseline in HbA1c at we	eek 52						
	Secondary outcomes:	Secondary outcomes:						
	- Change in total body weight							
	- Proportion with hypoglycaemic episode							
	- Proportion if ≥ 5% total weight loss.							
Participant	N: 801 analysed							
Criteria	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							
	receiving stable dose metrormin or metrormin and one other OAD at up to hair maximal dose for up to 8 weeks prior to enrolling, fasting plasma glucose \$150mm/y.							
	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 norma							
	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	pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin							
Interventions	pressure ≥110 mmHg; significant other disease.							
Interventions	pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin	d ≤10 g/dL for women; abnormal TSH; systolic blood pressu						
Interventions	pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prior to rance	d ≤10 g/dL for women; abnormal TSH; systolic blood pressu	ure ≥180mmHg and/or diastolic blood					
	pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prior to rance All groups: Patients randomly assigned to double blind therapy, e	d ≤10 g/dL for women; abnormal TSH; systolic blood pressu domization. either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pa	ure ≥180mmHg and/or diastolic blood					
Quality	pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prior to rance All groups: Patients randomly assigned to double blind therapy, e  Study Quality: medium – See Quality table for further information	d ≤10 g/dL for women; abnormal TSH; systolic blood pressu domization. either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pa n	ure ≥180mmHg and/or diastolic blood					
Quality Participant	pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prior to rance All groups: Patients randomly assigned to double blind therapy, e  Study Quality: medium – See Quality table for further information Group 1 (start n= 406, analysed n=400):	d ≤10 g/dL for women; abnormal TSH; systolic blood pressudomization.  either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pand	ure ≥180mmHg and/or diastolic blood					
Quality	pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prior to rance All groups: Patients randomly assigned to double blind therapy, estudy Quality: medium – See Quality table for further information Group 1 (start n= 406, analysed n=400):  2.5mg dapagliflozin + metformin	d ≤10 g/dL for women; abnormal TSH; systolic blood pressudomization.  bither, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pands  Group 2 (start n= 408, analysed n= 401)  5mg glipizide + metformin	ure ≥180mmHg and/or diastolic blood					
Quality Participant	pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prior to rance All groups: Patients randomly assigned to double blind therapy, estudy Quality: medium – See Quality table for further information Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin  Age: 58 SD 9 years	d ≤10 g/dL for women; abnormal TSH; systolic blood pressudomization.  bither, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pan  Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin  Age: 59 SD 10 years	ure ≥180mmHg and/or diastolic blood					
Quality Participant	pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prior to rand All groups: Patients randomly assigned to double blind therapy, e  Study Quality: medium – See Quality table for further information Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin Age: 58 SD 9 years Sex: 55.3% Male	d ≤10 g/dL for women; abnormal TSH; systolic blood pressund domization.  either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pain  Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin  Age: 59 SD 10 years Sex: 54.9§% Male	ure ≥180mmHg and/or diastolic blood					
Quality Participant	pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prior to rance All groups: Patients randomly assigned to double blind therapy, estudy Quality: medium – See Quality table for further information Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin  Age: 58 SD 9 years	d ≤10 g/dL for women; abnormal TSH; systolic blood pressudomization.  bither, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pan  Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin  Age: 59 SD 10 years	ure ≥180mmHg and/or diastolic blood					
Quality Participant	pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prior to rand All groups: Patients randomly assigned to double blind therapy, e  Study Quality: medium – See Quality table for further information Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin  Age: 58 SD 9 years Sex: 55.3% Male BMI (KG/M²): 31.7 SD 5.1 ≥ 25 kg/m²: 95%%	d ≤10 g/dL for women; abnormal TSH; systolic blood pressured	ure ≥180mmHg and/or diastolic blood					
Quality Participant	pressure ≥110 mmHg; significant other disease.  Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prior to rance All groups: Patients randomly assigned to double blind therapy, estudy Quality: medium – See Quality table for further information Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin  Age: 58 SD 9 years  Sex: 55.3% Male  BMI (KG/M²): 31.7 SD 5.1	domization. either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pan  Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin  Age: 59 SD 10 years Sex: 54.9§% Male BMI (KG/M²): 31.2 SD 5.1	ure ≥180mmHg and/or diastolic blood					

	FPG (mmol/l): 9.0 SD 2.1		FPG (mmol/l): 9.1 SD 2.3			
Outcome (change	from baseline at study end)					
	<b>Group 1</b> (start n= 406, analysed n=40 2.5mg dapagliflozin + metformin	0):	<b>Group 2 (</b> 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	-	-	-	-		
		<u></u>		·		
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  Group 2  At least one or more adverse of Group 1 = n=318  Group 2 = n=318  No deaths in Dapagliflozin group 3 deaths in Glipizide group			
Specific Events	<b>Group 1</b> UTI: n=44, GTI n = 50,		UTI: n=26, GTI n = 11,			
	HypoM n= 0 HypoS n= 7 HypoO, n=7 Events Leading to Discontinuation, n=	÷0	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 Activit	ies (MedDRA v12.1) via patient questionnaire	and active questioning during visits		

Canagliflozin, a	olidori D, Zhao Y, Sha S, Arbit D, Usiskin K et al.  n inhibitor of sodium glucose co-transporter 2, improves glycaemic control, lowers body weight, and improves beta cell function in type 2 diabetes on background metformin	Funding source: Johnson and Johnson					
Diabetologia 20	10 53:[S349]	Placebo + metformin Vs SGLT2 Inhibitor + metformin OD Vs SGLT2 inhibitor BD + metformin OD Vs sitaglipitin OD + metformin					
	e safety, tolerability and efficacy of an alternative SGLT2 inhibitor Canagliflozin and remaining beta cell function, in DM type 2 patients ven as a monotherapy.	vho have inadequate glycaemic control					
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/M²): 31.5 HA1c (%): 7.7% Duration of Diabetes: - FPG (mmol/l): 9.0 Systolic BP: -						

	<b>Group 1</b> placeb		<b>Group 2</b> canagliflozin 50mg + Metformin		Group 3 canag	liflozin 100mg + metformin	Group 4 can metformin	agliflozin 200mg +	
	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 canagi	iflozin 300mg + metformin	Group 6 canagli metformin	flozin 300mg BD +	Group 7 sitagli	iptin + metformin			
	Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)	1		
Δ HbA1c (%)	-0.71	-	-0.73	-	-0.56	-	1		
Δ Weight (kg)	-2.3	-	-2.3	_	+0.4	-	1		
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 balance	ed across all arms s	save for:	(0)				
Specific Events	Genital tract infections:UTIHypoglycaemia (not defined in abstract)3-8% canagliflozin arms3-9% canagliflozin armsabstract)2% placebo0-6% canagliflozin arms2% sitagliptin2% sitagliptin2% placebo5% sitagliptin5% 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 ad	verse events from the Medic	al Dictionary or Reg	gulatory Activities (Med	IDRA v12.1) via p	patient questionnaire and act	ive questionin	g during visits	

	ı KH, Hruba V, Elze M, Langkilde AM, Parikh S. gliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomiz	ad 24-week double-	Funding source: Astra-Zeneca and Bristol-Myers-Squibb				
	controlled trial.	eu, 24-week, double-	Bristor-wyers-squibb				
	Metab. 2011 13(10):[928-938]		2.5, 5, 10mg SGLT2 Inhibitor (dapagliflozin) vs 4mg glimepiride				
	nine efficacy, safety and tolerability of dapagliflozin treatment, as an add-on therapy to glimepiride, in patients v Ilphonylurea monotherapy	with inadequately contro	olled type 2 diabetes who had been				
Study	Multi Centre: 84 sites across 7 countries						
Particulars	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 <sup>2</sup>						
	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/m², 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 m titration allowed; in case of inadequate glycaemic control, patients could receive open-label rescue therapy of						
	dietary and lifestyle counseling and patients with BMI ≥27 kg/m <sup>2</sup> received advice regarding reducing caloric in						
Quality	Study Quality: Medium – See Quality table for further information	<u> </u>	·				
Participant	Group 1 (n= 146) Group 2 (n= 154) Group 3 (n= 145)		Group 4 (n= 151)				

baseline data	Placebo + glime	epiride	2.5mg dapagliflozin + glimepiride		5mg dapagliflozin + glimepiride		10mg dapagliflozin + glimepiride	
	Age (years): 60.3 SD 10.16 Sex: 49% male BMI (kg/m²) ≥ 25 kg/m²: 86.2%		Age (years): 59.9.3 SD 10.14 Sex: 50% male BMI (kg/m²)		Age (years): 60.2 SD 9.73 Sex: 50% male BMI (kg/m²)		Age (years): 58.9 SD 8.32 Sex: 43.7% male BMI (kg/m²)	
			≥ <b>25 kg/m²</b> : 84	.4%	≥ <b>25 kg/m²</b> : 78	3%	≥ 25 kg/m <sup>2</sup> : 1	79.4%
	≥ 30 kg/m <sup>2</sup> : 45.	.5%	≥ 30 kg/m <sup>2</sup> : 48	%	≥ <b>30 kg/m²:</b> 50	0%	≥ 30 kg/m <sup>2</sup> :	45.%
	HbA1c (%): 8.1		<b>HbA1c (%):</b> 8.1		HbA1c (%): 8.1		HbA1c (%): 8	
		abetes (years): 7.4SD 5.7		ibetes (years): 7.7 SD		abetes (years): 7.4 SD 5.7		diabetes (years): 7.2 SD 5.5
	FPG (mmol/L):		6.0	0.50 00.242	FPG (mmol/L):			L): 9.55 SD 2.04
	Systolic BP (mr	nHg): 133.3	FPG (mmol/L): Systolic BP (mr	,	Systolic BP (mi	<b>мнg):</b> 130.9	Systolic BP (I	mmHg): 133.8 SD 15
Outcome (chan	ge from baseline	at study end)	Systolic Di (IIII	1116/. 134.0				
	Group 1 (n= 14		Group 2 (n= 15	4)	Group 3 (n= 14	15)	Group 4 (n=	151)
	Placebo + glime		2.5mg dapaglif	lozin + glimepiride	5mg dapagliflo	zin + glimepiride	10mg dapagl	iflozin + glimepiride
	Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)
Δ from baseline	-0.13	-	-0.58	-0.61 to -0.27	-0.63	-0.67 to -0.32	-0.82	-0.86 to -0.51
HbA1c (%)								
Δ from baseline	-0.72	-	-1.18	-1.08 to +0.15	-1.56	-1.47 to -0.21	-2.26	-2.17 to -0.92
Weight (kg) Δ from	-0.33		-2.08	-2.50 to -1.00	-1.78	-2.20 to -0.68	-1.94	-2.34 to 0.87
baseline FPG (mmol/L)	-0.33	-	-2.08	-2.50 to -1.00	-1.78	-2.20 to -0.08	-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	-	-	-	-	-	-/	-	-
	<u> </u>	·		•			•	<u>'</u>
Adverse Events	UTI = Urinary 1	General events – where frequency is ≥3% in any group UTI = Urinary Tract Infection				Hypoglycaemia defined as blood sugar <70mg/dl)		<b>or more adverse event</b> 69
	GTI = Genital T						Group 2 = n=	
	Hypo = Hypogl	iycaemia					<b>Group 3 =</b> n= <b>Group 4 =</b> n=	
								apagliflozin 2.5mg apagliflozin 10mg
_	Group 1 (n= 14	46)	Group 2 (n= 15	4)	Group 3 (n= 14	15)	Group 4 (n=	• •
	3.00P = ( I	· - /	Group 2 (11- 134)		Group 3 (II- 143)		G100p + (11- 131)	

	Placebo + glimepiride	2.5mg dapagliflozin + glimepiride	5mg dapagliflozin + glimepiride	10mg dapagliflozin + glimepiride		
Specific Events	UTI: n=9, GTI n = 1,	UTI: n=6, GTI n = 6,	UTI: n=10, GTI n = 9,	UTI: n=8, GTI n = 10,		
	≥ 1Hypo n= 7	≥ 1Hypo n= 11	≥ 1Hypo n= 11	≥ 1Hypo n= 12		
	Bronchitis n= 4	Bronchitis n= 2	Diarrhoea n= 2	Bronchitis n= 5		
	Diarrhoea n= 5	Diarrhoea n= 4	Back pain n= 3	Diarrhoea n= 0		
	Back pain n= 4	Back pain n= 3	Nasopharyngitis n= 8	Back pain n= 7		
	Nasopharyngitis n= 4	Nasopharyngitis n= 3	Arthralgia n= 0	Nasopharyngitis n= 5		
	Arthralgia n= 4	Arthralgia n= 6	Upper resp. Tract Infection n= 6	Arthralgia n= 1		
	Upper resp. Tract Infection n= 4	Upper resp. Tract Infection n= 5	Hypertension n= 2	Upper resp. Tract Infection n= 4		
	Hypertension n= 6	Hypertension n= 8		Hypertension n= 2		
Safety	Assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits					
Assessment						

Wilding JPH, Norwo	od P, T <sup>1</sup> joen C, Bastien A, List JF, Fiedorek FT.	Funding source: Astra-Zeneca and
A Study of Dapaglifi independent treatn	Bristol-Myers-Squibb	
Diabetes care 2009	32(9):[1656-1662]	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 a	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	N: 65 analysed	
Criteria	Inclusion criteria: Participants aged between 18 years and 75; type 2 diabetes, BMI ≤45 kg/m², HbA1c of 7.5-10.0%; taking stab 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-creatini 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, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal, creatine kinase ≥3 times the upper limits of normal kinase ≥3 times the up	nits of normal, symptoms of severely
Interventions	Intervention 1: placebo plus stable dose of insulin sensitizer (metformin and/or pioglitazone) plus insulin (50% of p	ore-study dose)

	Intervention 2: 10	O mg dapagliflozin once daily plu	ıs 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						
	<b>Lead in period:</b> 10-21 day to establish reduced insulin dose						
Quality	•	lium – See Quality table for further					
Participant	Group 1 (n analyse	d=19):	Group 2 (n= 23):		Group 3 (n= 23):		
baseline data	Placebo, OADs + in	sulin,	10mg dapagliflozir	n, OADs + insulin,	20mg dapagliflozi	n OD, OADs + insulin,	
	Age (years): 58.4 SI	0 6.5	Age (years): 55.7 S	SD 9.2	Age (years): 56.1	SD 10.6	
	Sex: 69.6% male		<b>Sex:</b> 54.2% male		Sex: 54.2% male		
	BMI (kg/m²): 34.8 S	SD 4.6	BMI (kg/m <sup>2</sup> ): 35.5	SD 3.6	BMI (kg/m²): 36.2	2 SD 4.6	
	HbA1c (%): 8.40% S	D 0.9	HbA1c (%): 8.4% S	D 0.7	HbA1c (%):8.5% S	D 0.9	
	Duration of diabete	es (years): 7.4SD 5.7	Duration of diabet	tes (years): 11.8 SD 5.8	Duration of diabe	tes (years): 11.3 SD 5.6	
	FPG (mmol/L): 9.22	2 SD 2.86	FPG (mmol/L): 8.6	57 SD 2.17	FPG (mmol/L): 8.9	98 SD 3.06	
	Systolic BP (mmHg)	): n/a	Systolic BP (mmHg	g): n/a	Systolic BP (mmHg): n/a		
Outcome (change	from baseline at study	•					
	Group 1 (n analyse	d=19):	Group 2 (n= 23):		Group 3 (n= 23):		
	Placebo, OADs + in	sulin,	10mg dapagliflozir	n, OADs + insulin,	0 1 0	n 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 hynoglycaen	nia = symptomatic episode,	General events – v	where frequency is >5%	At least one or me	ore adverse event	
Adverse Events	capillary glucose <3		UTI = Urinary Tract Infection		<b>Group 1 =</b> n=15	ore daverse event	
	, , ,	nia = symptomatic episode,	GTI = Genital Tract		<b>Group 2 =</b> n=18		
		sistance with following recovery,	HypoT = Hypotens		<b>Group 3 =</b> n=16		
	capillary glucose <3		HypoG = Hypoglycaemia		One patient in each group discontinued due to		
	, 9, marca		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		adverse effects	g p	
Specific Events	Group 1 (n analyse	d=19):	Group 2 (n= 23): 10mg dapagliflozin, OADs + insulin,		Group 3 (n= 23): 20mg dapagliflozin OD, OADs + insulin,		
	Placebo, OADs + in						
	UTI: n=0. GTI n = 1.	,	UTI: n= 0, GTI n = 0	· · · · · · · · · · · · · · · · · · ·	UTI: n= 1, GTI n =		
	HypoT n=n/a, Hypo	G n=3	HypoT n=n/a, Hypo		HypoT n=n/a, Hyp	-	
	Nausea n= 1		Nausea n= 1		Nausea n= 3		
	Pollakiuria n= 4		Pollakiuria n= 2		pollakiuria n= 3		
	Back pain n= 2		Back pain n= 3		vomiting n=3		
	Nasopharyngitis n=	2	Nasopharyngitis n	= 2		Vulvovaginal mycotic infection n=3	
	Abdominal pain n=		Fatigue n= 2		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							

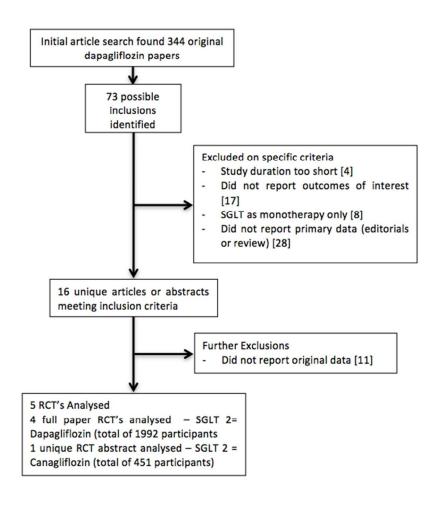


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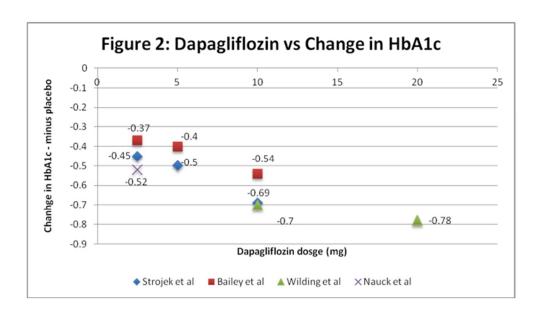
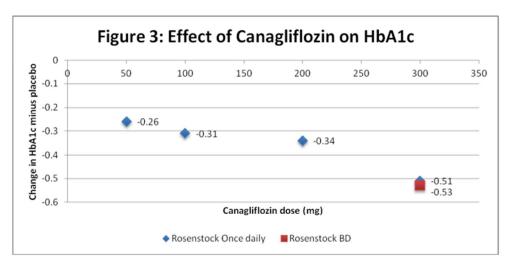
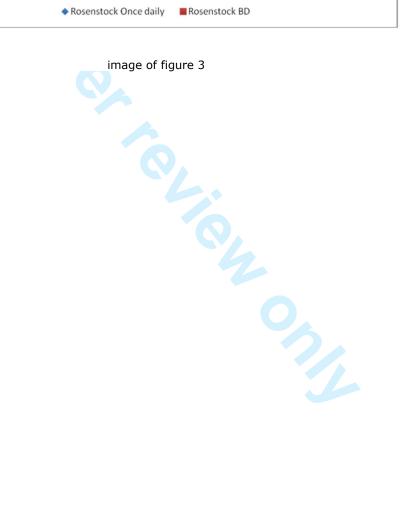


image of figure 2





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

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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	•		
2 Structured summary 3 4	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
3 Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7



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٠.				
4	Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency	N/A
5			(e.g., I <sup>2</sup> ) for each meta-analysis.	
b'				

Page 1 of 2			
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
FESULTS			
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
20 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			
Symmary 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
6 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
S& Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12
FUNDING			
1 12 Funding 13	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



#### 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	Fair points, but we can only report what research
discussing the SGTL2	there is.
receptor inhibitors used as combination therapy	And it is not correct that only one trial had an
for treatment of type	active comparator – there were two active
2 diabetes. While this is an important topic as we	comparators, glipizide in Nauck 2011 and
need to know what	sitagliptin in Rosenstock 2010.
is the best 2nd and 3rd line agent for type 2	Stagnpen in Noscristock 2010.
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.	
1) The introduction needs to address why this	Section added at end of Introduction with
topic needed a	similar message to referee's comments, and
systematic review. i.e. Few people know about	mentioning safety.
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	
critically stitle you do also	

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.
2) The discussion talks shout the lock of laws	We have added a paragraph on the FDA review
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	Figures for HbA1c changes added to Abstract.  No change to "good quality" – it's a standard expression in systematic reviews.
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.	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,	We have amended the structure slightly by having bolder headings for Introduction, Methods, Results, Discussion.
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 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.

	T
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	Paragraph removed – having expanded what is now the last paragraph of the Introduction, we no longer need the "Decision problem" section.
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.	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.  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	Categories retained because this was to address a specific hypothesis  OK, done, and subheading removed.
detail below".	
14) Study selection: would add the words	OK, done
inclusion/exclusion before the word criteria for clarity.	
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	Changed from "independently verified" to "checked".
someone's else's answers in which case it would	<b>Y</b> ,
be a serial not an	
independent review.	
16) Usually the Figure 1 has two boxes above the one listed there. One	The sources of data are in the text.
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 of figure amended and text below moved to start of Results.
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.	
17) Would move results header to above the	Results heading moved, but most subheadings

Ok, moved to Adverse events section
Fair point. Sentence deleted.
No change. There could be ceiling effects in adverse events too
OK, text revised and we have added the figures from Nauck, the largest study and calculated percentages and CIs.
Safe bit removed and paragraph on FDA review added.  Done.

from the sentence and	
would state effective at reducing a1c and weight in short term RCTs.	
in short term NC13.	
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	A meta-analysis would have been entirely inappropriate because of the heterogeneity of the studies.
not appropriate to draw these conclusions. A meta-analysis should be conducted and would substantially improve the paper.	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	Figures were as calculated in original studies.
package was used to get to this value? This value should be obtained using meta-analysis.	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 dosagebetween 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.	Ţ
The presentation of the results in this review needs to be revised.  This could be achieved by conducting a meta-analysis. Data could then	We remain convinced that a meta-analysis would not be appropriate.
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.	

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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.

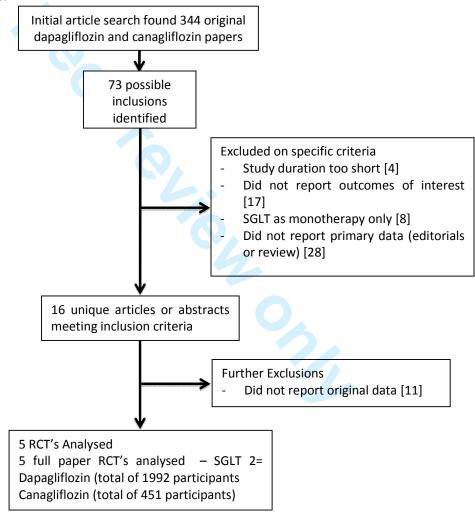
#### Data synthesis and analysis

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.

Table 1: Summary of trials (selected arms only) and change in HbA1c.					
Study	SGLT2	Comparator	Baseline	Change in	Difference
	inhibitor		HbA1c	HbA1c	
Bailey 2010	dapaglifozin	Placebo	dap 7.9%	- 0.84%	0.54%
(8)	10mg +	+ metformin	pbo 8.0%	- 0.3%	
	metformin				
Nauck 2011	dapagliflozin	glipizide 5mg	dap 7.7%	- 0.52%	No
(9)	2.5mg +	+ metformin	glip 7.7%	- 0.52%	difference
	metformin				
Rosenstock	canagliflozin	sitagliptin	can 7.7%	- 0.71%	0.15%
2010 (10)	300mg once		sita 7.7%	- 0.56%	
	daily				
Strojek 2011	dapaglifozin	glimepiride	dap 8.07%	- 0.82%	0.69%
(11)	10mg +	4mg +	pbo 8.15%	- 0.13%	
	glimepiride	placebo			
	4mg				
Wilding 2009	dapaglifozin	Placebo +	dap 8.4%	- 0.61%	0.7%
(12)	10mg+	insulin +	pbo 8.4%	+ 0.09%	
	insulin +	metformin or			
	metformin or	pioglitazone			
	pioglitazone				

#### **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  $32.7\text{kg/m}^2$  (range  $31.2-36.27\text{kg/m}^2$ ) 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% (0,44-0.60)	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	

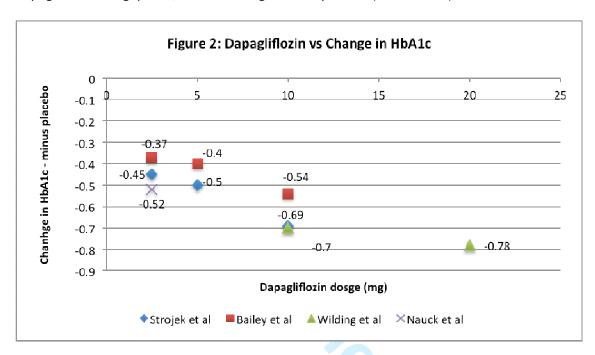
No p value or CI given for difference for sitaglitpin and canaglifozin; no CI for individual changes in Hba1c

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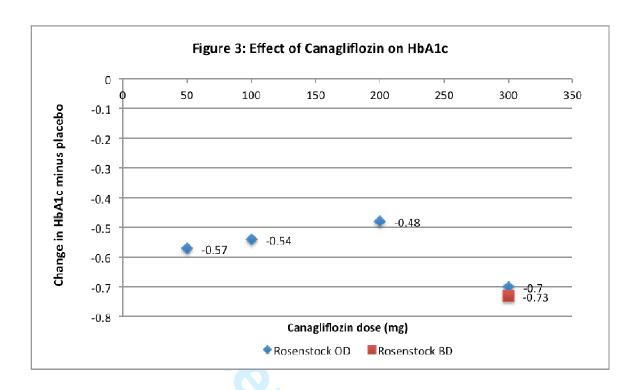
#### **HbA1c Levels**

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% Cl: -3.5 to -5.5) (Wilding), compared to a reduction of +1.9kg (95% Cl: 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% Cl -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 1<sup>st</sup> 2011)

- 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

 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 1<sup>st</sup> 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 20<sup>th</sup> 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

 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 cotransport (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

Effect of Dapag	s JL, Pieters A, Bastien A, List JF. gliflozin in patients with type 2 diabetes wh	o have inadequate glycaemic control with	metformin: a randomised, double-blind,	Funding source: Astra-Zeneca and Bristol-Myers-Squibb				
placebo-contro Lancet 2010 (3	olled trial. 75):[2223-2233]			SGLT2 Inhibitor Vs. metformin				
Aim: Determin	e if dapagliflozin, lowers HbA1c in type 2 dia	betes in patients with inadequate HbA1c co	ntrol with metformin					
Study	Multi Centre: 81							
Particulars	Duration of intervention: 24 weeks							
	Duration of run in: 2 weeks							
	Follow-up: on completion of 24 weeks, a	102 week long-term study						
	<b>Design:</b> 4-arm RCT, double blind, placebo	controlled						
	Duiman, autama, Changa franchasalina i	a Lib A 1 a at week 2.4						
	<b>Primary outcome:</b> Change from baseline i	II HDAIC at Week 24						
	Secondary outcomes:							
	At 1 week, change in fasting plasma glucose							
	At 24 weeks changes in:							
	Fasting plasma     Proportion of patients achieving a therapeutic HbA1c, and							
	Glucose concentration     Total bodyweight      Total bodyweight							
	<ul> <li>No. with baseline HbA1c of 9% or more.</li> <li>Change from baseline in bodyweight, and decreases in bodyweight of 5% or more.</li> </ul>							
Participant	N: 534 analysed	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	7 9 9					
Criteria	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 normal; symptoms of normal displaces (including marked polyuris and polyding) with \$10% weight less during the 2 months before enrollment); and syntalic blood prossure 190 mm. He							
	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		naomisea successiai esmipienem meno	in acceptabilities to 1 Issuella				
Participant	Group 1 (n analysed=134):	Group 2 (n= 135):	Group 3 (n= 133):	Group 4 (n= 132):				
baseline data	Placebo OD + metformin,	2.5mg dapagliflozin OD, metformin	5mg dapagliflozin OD, metformin	10mg dapagliflozin OD, metformin				
	<b>Age:</b> 53.7 SD 10.3 years	<b>Age:</b> 55.0 SD 9.3 years	<b>Age:</b> 54.3 SD 9.4 years	<b>Age:</b> 52.7 SD 9.9 years				
	Sex: 55% Male	Sex: 51% Male	Sex: 50% Male	Sex: 57% male				
	BMI (KG/M <sup>2</sup> ): 31.8 SD 5.3	<b>BMI (KG/M<sup>2</sup>):</b> 31.6 SD 4.8	<b>BMI (KG/M²):</b> 31.4 SD 5.0	BMI (KG/M <sup>2</sup> ): 31.2 SD 5.1				
	<b>HbA1c (%):</b> 8.11% SD 0.96	<b>HbA1c (%):</b> 8.96% SD 2.39	<b>HbA1c (%):</b> 8.17% SD 1.0	<b>HbA1c (%):</b> 7.92% SD 0.82				
	<b>Duration of Diabetes:</b> 5.8 SD 5.1	<b>Duration of Diabetes:</b> 6.0 SD 6.2	<b>Duration of Diabetes:</b> 6.4 SD 5.8	<b>Duration of Diabetes:</b> 6.1 SD 5.4				

	FPG (mmol/l): 9.19 SD 2.57 Systolic BP: 127.7 SD 14.6			): 8.96 SD 6.2 126.6 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 (chan	 nge from baseline	e at study end)						
	Group 1 (n ana Placebo OD + r	lysed=134):	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
		<pre>ycaemia = symptomatic episo very, capillary glucose &lt;3.0mr</pre>	de, needing external assistance with mol/l)  Group 2 (n= 135): 2.5mg dapagliflozin OD, metformin		UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoT = Hypotension HypoG = Hypoglycaemia Group 3 (n= 133): 5mg dapagliflozin OD, metformin		Group 2 = n=89 Group 3 = n=95 Group 4 = n=98 Group 4 (n= 132): 10mg dapagliflozin OD,	
	Group 1 (n and Placebo OD +	-						
Specific	UTI: n= 11, GT	•	UTI: n= 6 GTI		UTI: n= 10, GTI n = 18		UTI: n= 16, GTI n =12,	
Events	HypoT n=1, Hy Diarrhoea n= 7 Back pain n= 7	7	HypoT n=0, F Diarrhoea n= Back pain n=	3	HypoT n=2, Hypo Diarrhoea n= 5 Back pain n= 3	ou n=5,	HypoT n=0, F Diarrhoea n= Back pain n=	: 10
	Nasopharyngit		Nasopharyng Cough n= 4		Nasopharyngitis Cough n= 4	n=4	Nasopharyng Cough n= 1	
	Influenza n= 1	0	Influenza n=	13	Influenza n= 13		Influenza n=	8
	Hypertension n= 6 Upper resp. Tract Infection n= 10		Hypertension n= 9 Upper resp. Tract Infection n= 5		Hypertension n= 4 Upper resp. Tract Infection n= 4		Hypertension Upper resp.	n n= 5 Tract Infection n= 3
Safety Assessment	Headache n= 6 Assessed via a	dverse events from the Medic	Headache n= cal Dictionary or		Headache n= 1 dDRA v12.1) via pa	tient questionnaire and	Headache n= active questioni	

· ·	o S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al pizide as Add-on Therapy in Patients with Type 2 diabetes	who have inadequate glycaemic control with Metformin	Funding source: Astra-Zeneca and Bristol-Myers-Squibb					
Diabetes care 2011	54.[2015-2022]		SGLT2 Inhibitor + metformin vs metformin + glipizide					
Aim: Compare effic	acy, 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							
	<b>Duration of intervention</b> : 52 weeks							
	Duration of run in: 2 weeks							
	<b>Followup:</b> on completion of 52 weeks, a 156 week long-to	erm study						
	Design: 2-arm parallel group, RCT.							
	Primary outcome: Absolute change from baseline in HbA	1c at week 52						
	Secondary outcomes:							
	- Change in total body weight							
	- Proportion with hypoglycaemic episode							
	- Proportion if ≥ 5% total weight loss.							
Participant	N: 801 analysed							
Criteria	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.		c and, or alastone blood					
Interventions			e ====================================					
interventions	Intervention 1: 2.5mg dapagliflozin + metformin							
	Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin		2					
	Intervention 2: 5mg glipizide + metformin							
	Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prio							
Quality	Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prio All groups: Patients randomly assigned to double blind the	nerapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pati						
•	Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prio All groups: Patients randomly assigned to double blind th  Study Quality: medium – See Quality table for further inf	nerapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pati formation						
Participant	Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prio All groups: Patients randomly assigned to double blind th  Study Quality: medium – See Quality table for further inf  Group 1 (start n= 406, analysed n=400):	nerapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All patiformation  Group 2 (start n= 408, analysed n= 401):						
· •	Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prio All groups: Patients randomly assigned to double blind th  Study Quality: medium – See Quality table for further inf  Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin	nerapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pati formation  Group 2 (start n= 408, analysed n= 401): 5mg glipizide + metformin						
Participant	Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prio All groups: Patients randomly assigned to double blind th  Study Quality: medium – See Quality table for further inf  Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin  Age: 58 SD 9 years	nerapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pati formation  Group 2 (start n= 408, analysed n= 401): 5mg glipizide + metformin  Age: 59 SD 10 years						
Quality Participant baseline data	Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prio All groups: Patients randomly assigned to double blind the Study Quality: medium – See Quality table for further inf Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin  Age: 58 SD 9 years Sex: 55.3% Male	nerapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pati formation  Group 2 (start n= 408, analysed n= 401): 5mg glipizide + metformin  Age: 59 SD 10 years Sex: 54.9§% Male						
Participant	Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prio All groups: Patients randomly assigned to double blind th  Study Quality: medium – See Quality table for further inf  Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin  Age: 58 SD 9 years	nerapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pati formation  Group 2 (start n= 408, analysed n= 401): 5mg glipizide + metformin  Age: 59 SD 10 years						
Participant	Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prio All groups: Patients randomly assigned to double blind the Study Quality: medium – See Quality table for further infi Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin  Age: 58 SD 9 years Sex: 55.3% Male BMI (KG/M²): 31.7 SD 5.1	formation  Group 2 (start n= 408, analysed n= 401): 5mg glipizide + metformin  Age: 59 SD 10 years Sex: 54.9§% Male BMI (KG/M²): 31.2 SD 5.1						
Participant	Intervention 2: 5mg glipizide + metformin  Lead in period: 2 weeks, single blind placebo lead in prio All groups: Patients randomly assigned to double blind th Study Quality: medium – See Quality table for further inf Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin  Age: 58 SD 9 years Sex: 55.3% Male BMI (KG/M²): 31.7 SD 5.1 ≥ 25 kg/m²: 95%%	nerapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All patiformation  Group 2 (start n= 408, analysed n= 401): 5mg glipizide + metformin  Age: 59 SD 10 years Sex: 54.9§% Male BMI (KG/M²): 31.2 SD 5.1 ≥ 25 kg/m²: 90.7%						

	FPG (mmol/l): 9.0 SD 2.1		FPG (mmol/I): 9.1 SD 2.3			
Outcome (change 1	irom baseline at study end)					
	<b>Group 1</b> (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin		<b>Group 2 (</b> 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) = syr <3.5mmol/l)	nptomatic episode, capillary glucose	General events – where frequency is ≥3%	At least one or more adverse event Group 1 = n=318		
	Severe hypoglycaemia (HypoS) = syn assistance with following recovery, co	apillary glucose <3.0mmol/l)	UTI = Urinary Tract Infection GTI = Genital Tract Infection	<b>Group 2 =</b> n=318		
	Other hypoglycaemia (HypoO) = sym confirming	ptoms, but without measurement	HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia other	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		UTI: n=26, GTI n = 11, HypoM n= 3			
	Events Leading to Discontinuation, no	=0	Events Leading to Discontinuation, n=6			
	Diarrhoea n= 19 Nausea n= 14		Diarrhoea n= 26 Nausea n= 15			
	Vulvovaginal mycotic infection n= 14 Back pain n= 19		Vulvovaginal mycotic infection n= 2 Back pain n= 20			
	Nasopharyngitis n= 43 Cough n= 15 Influenza n= 30		Cough n= 20	Influenza n= 30 Pain in extremity n= 21		
	Pain in extremity n= 11		Pain in extremity n= 21			
	Upper resp. Tract Infection n= 24 Headache n= 21		Upper resp. Tract Infection n= 17 Headache n= 17			
	Hypertension n= 30		Hypertension n= 35			
Safety Assessment	Assessed via adverse events from the	Medical Dictionary or Regulatory Activit	ies (MedDRA v12.1) via patient questionnaire	and active questioning during visits		

Dose-Ranging E	ggarwal N, Polidori D, Zhao Y, Sha S, Arbit D, Usiskin K et al.  Effects of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-On to Metformin in Subjects With Type 2 Diabetes	Funding source: Johnson and Johnson
	<b>une 2012</b> vol. 35 no. 6 <b>1232-1238</b>	Placebo + metformin vs SGLT2 Inhibitor + metformin OD Vs SGLT2 inhibitor BD + metformin OD Vs sitaglipitin OD + metformin
	esafety, tolerability and efficacy of an alternative SGLT2 inhibitor Canagliflozin and remaining beta cell function, in DM type 2 patients nas a monotherapy.	s who have inadequate glycaemic control
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 Ol	D 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 subjeweeks. Finally the assessment of the loss of beta cell function measured using HOMA2-B% derived from plasma glucose and C pept	
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 inadec monotherapy, stable body weight, BMI 25-45, serum creatinine <1.5mg/dl for men, <1.4mg/dl for women	quate glycaemic control using metformin
	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	<b>Age:</b> 53	•
baseline data	Sex: male 52%	
	BMI (KG/M²): 31.5	
	HA1c (%): 7.7%	
	Duration of Diabetes: -	
	FPG (mmol/l): 9.0	
	Systolic BP:	
Outoom o /sh - :-	and from benefiting at attacks and \	
Outcome (chan	ge from baseline at study end)	

	Group 1 placebo + metformin (n=55)		Group 2 o		zin 50mg +	<b>Group 3</b> canagliflozin 100mg + metformin (n=59)		<b>Group 4</b> canagliflozin 200mg + metformin (n=56)		
	Mean	Confidence (95%)	Mean		Confidence (95%)	Mean	Cor	fidence (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	0.8	5	6.9	0.68
	<b>Group 5</b> canaglifloz (n=56)	in 300mg + metformin	Group 6 o		zin 300mg BD +	Group 7 sitagl (n=60)	iptin + metfo	min		
	Mean	Confidence (95%)	Mean		Confidence (95%)	Mean	Con	fidence (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	episode, capillary g Severe hypoglycae episode, needing ex recovery, capillary g	nia (HypoM) = symptoma lucose <3.5mmol/l) mia (HypoS) = symptoma kternal assistance with fol glucose <3.0mmol/l) nia (HypoO) = symptoms, ent confirming	tic llowing	UTI = U GTI = G	al events – where fre Irinary Tract Infectio Genital Tract Infection Hypoglycaemia	n		At least one of Group 1 = n=1 Group 2 = n=2 Group 3 = n=2 Group 4 = n=2 Group 5 = n=1 Group 6 = n=2 Group 7 = n=1	1 5 6 4 9 5	e event
Specific	Group 1		Group 2			Group 3		7/1	Group 4	
Events	UTI: n=4, GTI n = 1		UTI: n=3,		•	UTI: n=2, GTI r			UTI: n=6, GT	•
	J	Discontinuation, n=1		•	Discontinuation,	Events Leading	g to Discontin	uation, n=3		ing to Discontinuation, n=1
	Hypo = 1		n=1 Hypo			Hypo = 1			Hypo = 4	
	Headache n= 2		Headache			Headache n= 5			Headache n=	
	Vulvovaginal mycot	ic infection n= 0	•	•	otic infection n= 4	Vulvovaginal n	nycotic infect	ion n= 2	_	I mycotic infection n= 4
	Nausea n= 0		Nausea n			Nausea n= 1			Nausea n= 1	
	Nasopharyngitis n=	2	Nasophar		= 5	Nasopharyngi			Nasopharyn	•
	Diarrhoea n= 2		Diarrhoea			Diarrhoea n= 3			Diarrhoea n=	
	Pollakiuria n = 1		Pollakiuri	ia n = 1		Pollakiuria n =	3		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,	UTI: n=3, GTI n = 4,	UTI: n=1, GTI n = 1,					
	Hypo = 0	Hypo = 2	Hypo = 3					
	Events Leading to Discontinuation, n=2	Events Leading to Discontinuation, n=2	Events Leading to Discontinuation, n=0					
	Headache n= 3	Headache n= 1	Headache n= 1					
	Vulvovaginal mycotic infection n= 1	Vulvovaginal mycotic infection n= 3	Vulvovaginal mycotic infection n= 1					
	Nausea n= 3	Nausea n= 5	Nausea n= 1					
	Nasopharyngitis n= 1	Nasopharyngitis n= 1	Nasopharyngitis n= 3					
	Diarrhoea n= 2	Diarrhoea n= 3	Diarrhoea n= 2					
	Pollakiuria n = 2	Pollakiuria n = 0	Pollakiuria n = 2					
	A/E associated with hypotension n= 1	A/E associated with hypotension n= 1	A/E associated with hypotension n= 1					
	Genital tract infections:	UTI	Hypoglycaemia					
	3-8% canagliflozin arms	3-9% canagliflozin arms	0-6% canagliflozin arms					
	2% placebo	6% placebo	2% placebo					
	2% sitagliptin	2% sitagliptin	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 Medic	cal Dictionary or Regulatory Activties (Med	DRA v12.1) via patient questionnaire and act	tive questioning during visits				

Strojek K, Yoor	ı KH, Hruba V, Elze M, Langkilde AM, Parikh S.	Funding source: Astra-Zeneca and
Effect of Dapa	gliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-	Bristol-Myers-Squibb
blind, placebo	controlled trial.	
Diabetes Obes	Metab. 2011 13(10):[928-938]	2.5, 5, 10mg SGLT2 Inhibitor (dapagliflozin) vs 4mg glimepiride
	nine efficacy, safety and tolerability of dapagliflozin treatment, as an add-on therapy to glimepiride, in patients with inadequately contro Ilphonylurea monotherapy	olled type 2 diabetes who had been
Study	Multi Centre: 84 sites across 7 countries	
Particulars	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 fr	om baseline to week 24							
	Secondary outcomes:								
	- Total body weight after 24 weeks								
		4 in post challenge plasma glucose (2hrs	) following oral glucose tolerance						
	<ul> <li>Proportion of patients with HBA1c</li> </ul>								
	Total body weight from baseline if	BMI ≥27kg/m²							
Participant	- FPG from baseline after 24weeks								
Criteria	N: 592 analyzed								
Criteria	Inclusion criteria: Participants aged 18 years	and older: inadequately controlled type	2 diahetes BMI <45kg/m <sup>2</sup> HhA1c of >7 to <	10.0%: on stable sulphonylurea dose (at					
	least half maximum dose (max 4 mg) for at le								
	3,757	1 1 1 1, 10 1, 10	, , , , , , , , , , , , , , , , , , , ,	,					
	Exclusion criteria: creatinine clearance <50 r								
	kinase ≥3 x upper limit of normal; total biliru		dL for men and ≤10 g/dL for women; abnorm	al TSH; SBP ≥180 mmHg and/or DBP ≥110					
	mmHg. Any significant other systemic diseas	e							
Interventions	Intervention 1: placebo plus 4 mg/day glime	piride		_					
	Intervention 2: 2.5 mg/day dapagliflozin plus								
	Intervention 3: 5 mg/day dapagliflozin plus 4								
	Intervention 4: 10 mg/day dapagliflozin plus	4 mg/day glimepiride							
	Lead in period: 1 week for inclusion/exclusion	on review for those switched to 4 mg/da	y glimepiride						
	All groups: dapagliflozin double-blind, glime	piride open label: glimeniride allowed to	he down-titrated to 2 mg/day or discontinue	d in case of hypoglycaemia, no un-					
	titration allowed; in case of inadequate glyca								
	dietary and lifestyle counseling and patients								
Quality	Study Quality: Medium – See Quality table for		<u> </u>	,					
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					
	<b>Age (years):</b> 60.3 SD 10.16	<b>Age (years):</b> 59.9.3 SD 10.14	Age (years): 60.2 SD 9.73	<b>Age (years):</b> 58.9 SD 8.32					
	Sex: 49% male	<b>Sex:</b> 50% male	Sex: 50% male	<b>Sex:</b> 43.7% male					
	BMI (kg/m²) ≥ 25 kg/m²: 86.2%	BMI (kg/m²) ≥ 25 kg/m²: 84.4%	BMI (kg/m²) ≥ 25 kg/m²: 78%	BMI $(kg/m^2)$ $\geq 25 kg/m^2$ : 79.4%					
	≥ <b>30 kg/m²:</b> 45.5%	≥ 30 kg/m <sup>2</sup> : 48%	≥ <b>30 kg/m²:</b> 50%	≥ <b>30 kg/m²:</b> 45.%					
	HbA1c (%): 8.15 SD 0.74	<b>HbA1c (%):</b> 8.11, SD 0.75	HbA1c (%): 8.12 SD 0.78	HbA1c (%): 8.07 SD 0.79					
	Duration of diabetes (years): 7.4SD 5.7	<b>Duration of diabetes (years):</b> 7.7 SD 6.0	Duration of diabetes (years): 7.4 SD 5.7 FPG (mmol/L): 9.68 SD 2.12	Duration of diabetes (years): 7.2 SD 5.5 FPG (mmol/L): 9.55 SD 2.04					
	FPG (mmol/L): 9.58 SD 2.07 Systolic BP (mmHg): 133.3	FPG (mmol/L): 9.56, SD 2.13	Systolic BP (mmHg): 130.9	Systolic BP (mmHg): 133.8 SD 15					
	Systolic Di (Illining). 133.3	Systolic BP (mmHg): 134.6	5,500 Dr (mmig). 130.3	3,500 DI (IIIIIII), 155.0 DE 15					
		3,300.00 Ji (iiiiii) 5,1 137.0							

	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	-	-	-	-	-	-	-	-
	Events General events – where frequency is ≥3% UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia				<70mg/dl)		Group 1 = n=69 Group 2 = n=80 Group 3 = n=70 Group 4 = n=76 1 death in Dapagliflozin 2.5mg	
	C 1 (n. 14)	c)	C	\ .	2 2/ /27			pagliflozin 10mg
	Group 1 (n= 140 Placebo + glime	=	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		UTI: n=6, GTI n =		UTI: n=10, GTI r		UTI: n=8, GTI	
	≥ 1Hypo n= 7	-,	≥ 1Hypo n= 11		≥ 1Hypo n= 11		≥ 1Hypo n= 12	
	Bronchitis n= 4		Bronchitis n= 2		Diarrhoea n= 2	<b></b>	Bronchitis n=	
	Diarrhoea n= 5		Diarrhoea n= 4		Back pain n= 3		Diarrhoea n=	0
	Back pain n= 4		Back pain n= 3		Nasopharyngiti	s n= 8	Back pain n=	7
	Nasopharyngitis	s n= 4	Nasopharyngitis	n= 3	Arthralgia n= 0		Nasopharyng	itis n= 5
	Arthralgia n= 4		Arthralgia n= 6		Upper resp. Tra	act Infection n= 6	Arthralgia n=	
	Linner rech Tra	ct Infection n= 4	Upper resp. Tract Infection n= 5		Hypertension n= 2		Upper resp. Tract Infection n= 4	
	Opper resp. 11a	Hypertension n= 6 Hypertension n= 8					Hypertension	

•	ood P, T'joen C, Bastien A, List JF, Fiedorek FT. flozin in Patients With Type 2 Diabetes Receiving High Do	ses of Insulin Plus Insulin Sensitizers. Applicability of a nove	Funding source: Astra-Zeneca and Bristol-Myers-Squibb				
independent treatn Diabetes care 2009	ment 32(9):[1656-1662]		SGLT2 Inhibitor + patients own oral antidiabetic drugs (OAD) Vs insulin + OAD				
Aim: Determine if [		with type 2 diabetes poorly controlled with high insulin dose	es 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	g-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%						
5	- Percentage of end patients with final HbA1c <	.1%					
Participant	N: 65 analysed	and 75, turns 2 dishetes DNAL <45 kg/m² Llb A1e of 7.5.10.00%	taking stable dasa matfarmin (>1000mm) and/ar				
Criteria	Inclusion criteria: Participants aged between 18 years and 75; type 2 diabetes, BMI ≤45 kg/m², 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						
	<b>Lead in period:</b> 10-21 day to establish reduced in		оодпусаенна				
Quality							
Quality	Study Quality: Medium – See Quality table for further i		Cycum 2 (n= 22):				
Participant baseline data	Group 1 (n analysed=19): Placebo, OADs + insulin,	, , ,	Group 3 (n= 23): 20mg dapagliflozin OD, OADs + insulin,				
vaseille uata	Flacebo, OADS + Illsuilli,	TOTHE dapagimozin, OADS + msulin,	come dapagimozini od, dads + insuini,				

Outcome (change f	Age (years): 58.4 SD 6.5  Sex: 69.6% male  BMI (kg/m²): 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  e from baseline at study end)  Group 1 (n analysed=19):		Age (years): 55.7 SI Sex: 54.2% male BMI (kg/m²): 35.5 SI HbA1c (%): 8.4% SI Duration of diabete FPG (mmol/L): 8.67 Systolic BP (mmHg	SD 3.6 0 0.7 <b>es (years):</b> 11.8 SD 5.8 7 SD 2.17	Sex: 54.2% male BMI (kg/m²): 36.2 HbA1c (%):8.5% S Duration of diabe FPG (mmol/L): 8.9	BMI (kg/m²): 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		
	Placebo, OADs + inst		10mg dapagliflozin,	. OADs + insulin.		n 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		
	capillary glucose <3.5mmol/L)  Major hypoglycaemia = symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/l)		UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoT = Hypotension HypoG = Hypoglycaemia		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		Group 2 (n= 23):		Group 3 (n= 23):	Group 3 (n= 23):		
	Placebo, OADs + inst	ılin,	10mg dapagliflozin, OADs + insulin, UTI: n= 0, GTI n = 0, HypoT n=n/a, HypoG n=7,			20mg dapagliflozin OD, OADs + insulin,		
	UTI: n=0, GTI n = 1,				UTI: n= 1, GTI n = !	•		
	HypoT n=n/a, HypoG	n=3			HypoT n=n/a, Hyp	oG n=6		
	Nausea n= 1		Nausea n= 1			Nausea n= 3		
	Pollakiuria n= 4		Pollakiuria n= 2		pollakiuria n= 3			
	Back pain n= 2		Back pain n= 3		vomiting n=3			
	Nasopharyngitis n= 2		Nasopharyngitis n=	2	Vulvovaginal myco	otic infection n=3		
	Abdominal pain n= 2		Fatigue n= 2		Anxiety n=2			
	Influenza n= 2		Influenza n= 1	2	Back pain n= 2			
	Pain in extremity n=		Pain in extremity n		Dry Mouth n=2	2		
	Upper resp. Tract Info	ection n= 2	Upper resp. Tract Ir Headache n= 3	nection n= 2	Nasopharyngitis n Peripheral odema			
	Procedural pain n=2		Pharyngolaryngeal	nain n=2	Abdominal pain n			
	1 Tocedural paint 11-2		i nai yngolai yngeal	paiii 11-2	Fatigue n= 1	-4		
					Influenza n= 1			
					Pain in extremity	n= 1		
					Upper resp. Tract			

Safety Assessment

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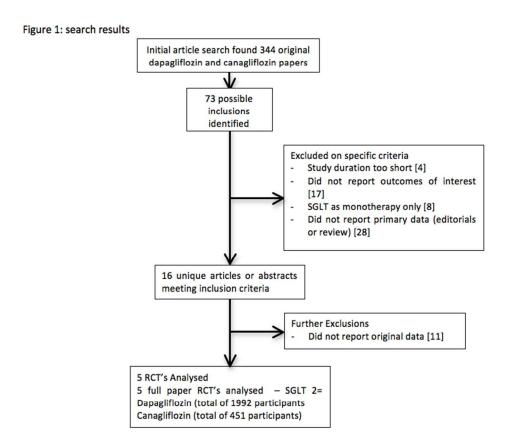
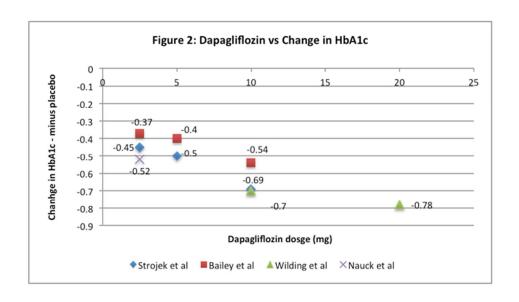
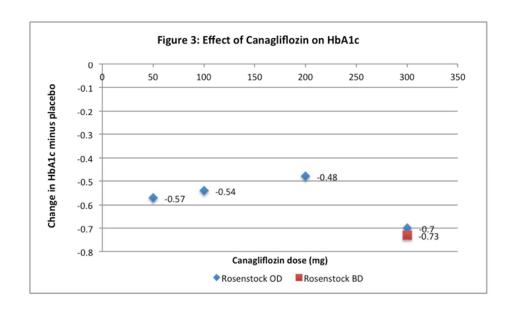


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258×143mm (72 x 72 DPI)







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

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Manuscript ID:	bmjopen-2012-001007.R3
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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. 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, <sup>2;3</sup> 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).<sup>4</sup>

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.<sup>5</sup>

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.<sup>6</sup>

#### **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.<sup>7</sup>

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
  - o 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<sup>6</sup> 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. 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<sup>2</sup> 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.

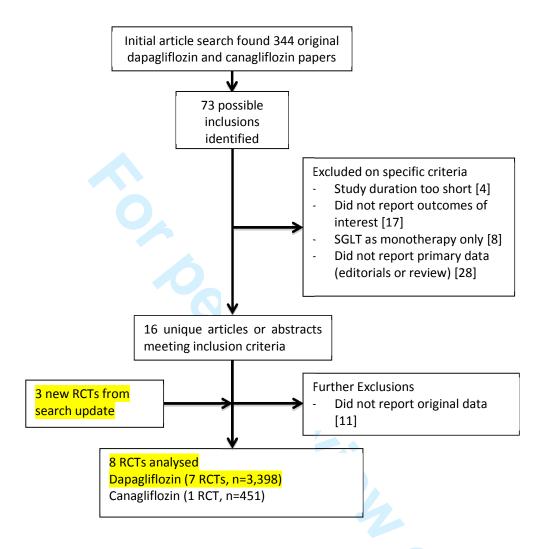
No meta-analysis using active comparators was performed due to clinical heterogeneity. Only two trials had active comparators, glipizide and sitagliptin, which have different modes of action and different effects on weight and hypoglycaemia risk.

#### **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.<sup>8-15</sup> The dapagliflozin trials included 3,398 participants. In the single canagliflozin trial, <sup>16</sup> 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)<sup>9</sup> 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,<sup>8;9;11;16</sup> insulin,<sup>15</sup> glimepiride,<sup>13</sup> thiazolidinedione (TZD),<sup>12</sup> or combination therapy.<sup>14;15</sup>

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

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

Study design	Participants	Interventions	Outcomes
Wilding 2009 <sup>14</sup>	N: 71	Intervention: 10 or 20 mg dapagliflozin	HbA1c (%): -0.70 (-1.07, -0.33)
Design: multi-centre (n=26), 3-arm,	Age (years): 56 to 58 SD7 to 11	once daily	Weight (kg): -2.60 (-3.94, -1.26)
double blind, placebo controlled RCT	<b>HbA1c (%):</b> 8.4 to 8.5 SD0.7 to 0.9	Comparator: placebo	FPG (mmol/L): -0.86 (-2.13, +0.42)
Duration: 12 weeks	<b>BMI (kg/m²):</b> 34.8 to 36.2 SD3.6 to 4.6	Background antidiabetic therapy:	SBP (mmHg): NR
Follow-up: 4 weeks		insulin (51 to 56 U) + OAD (≤79%	
Quality: medium		metformin only, ≤25% metformin plus	
		TZD, ≤12.5% TZD only)	
Wilding 2012 <sup>15</sup>	N: 800	Intervention: 2.5, 5 or 10 mg	<b>HbA1c (%):</b> -0.57 (-0.67, -0.40)
Design: multi-centre (n=126), 4-arm,	Age (years): 59 to 60 SD8 to 9	dapagliflozin once daily	Weight (kg): -2.04 (-2.57, -1.51)
double blind, placebo controlled RCT	<b>HbA1c (%):</b> 8.5 to 8.6 SD0.8 to 0.9	Comparator: placebo	FPG (mmol/L): NR
Duration: 24 weeks	<b>BMI (kg/m²):</b> 33.0 to 33.4 SD5.0 to 5.9	Background antidiabetic therapy:	SBP (mmHg): -3.11 (-5.79, -0.43)
Follow-up: 24 + 56 week extension		insulin (77.1 U) ± OAD (~50% none,	
Quality: high		~40% metformin only, rest combination)	
Canagliflozin			Difference versus active / placebo (95%
			CI)
Rosenstock 2012 <sup>16</sup>	N: 451	<b>Intervention:</b> 50, 100, 200 or 300 mg OD	<b>HbA1c (%):</b> -0.48 to -0.73 vs placebo;
Design: multi-centre (n=85), 7-arm,	Age (years): 52.9 SD8.1	or 300 mg BD canagliflozin	+0.04 to -0.21 vs sitagliptin (95% CI NR)
double blind, placebo and active	HbA1c (%): 7.75 SD0.93	Comparator 1: placebo	Weight (kg): -1.2 to -2.3 vs placebo;
controlled RCT	<b>BMI (kg/m²):</b> 31.5 SD4.9	Comparator 2: 100 mg OD sitagliptin	-1.7 to -2.8 vs sitagliptin (95% CI NR)
Duration: 12 weeks		Background antidiabetic therapy:	<b>FPG (mmol/L):</b> -1.1 to -1.7 vs
Follow-up: 2 weeks		metformin (≥1500 mg)	placebo; -0.2 to -0.8 vs sitagliptin (95%
Quality: medium			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 <sup>8</sup>	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 <sup>9;10</sup>	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 <sup>11</sup>	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 <sup>12</sup>	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 <sup>13</sup>	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 <sup>14</sup>	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 <sup>15</sup>	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 <sup>16</sup>	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)<sup>16</sup> 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)<sup>9</sup>. 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).

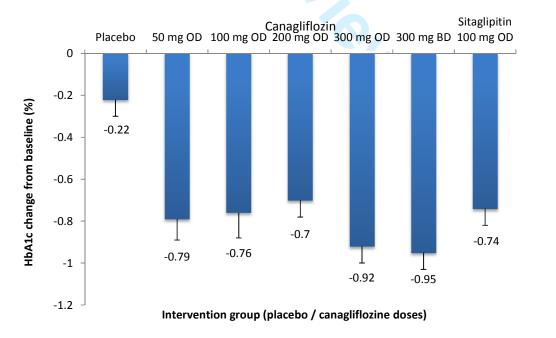
In the study by Nauck 2011,<sup>11</sup> there was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by -0.52% (95% CI: -0.60, -0.44).

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

	Dapaglif	lozin (10	mg)	Pla	cebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
1.1.1 up to 26 weeks									
Bailey 2010	-0.84	0.82	132	-0.3	0.83	134	10.1%	-0.54 [-0.74, -0.34]	<del></del>
Bolinder 2012	-0.39	0.46	83	-0.1	0.42	86	13.3%	-0.29 [-0.42, -0.16]	<del></del>
Rosenstock 2012	-0.97	0.67	140	-0.42	0.67	139	12.0%	-0.55 [-0.71, -0.39]	<del></del>
Strojek 2011	-0.82	0.75	150	-0.13	0.79	143	11.1%	-0.69 [-0.87, -0.51]	
Wilding 2009	-0.61	0.58	23	0.09	0.62	19	4.9%	-0.70 [-1.07, -0.33]	<del></del>
Wilding 2012 Subtotal (95% CI)	-0.96	0.67	173 <b>701</b>	-0.39	0.72	166 <b>687</b>	12.5% <b>63.9%</b>	-0.57 [-0.72, -0.42] -0.54 [-0.67, -0.40]	•
1.1.2 48 weeks and m	nore	,							
Bolinder 2012	-0.38	0.51	79	0.02	0.51	77	11.9%	-0.40 [-0.56, -0.24]	
Rosenstock 2012	-1.21	0.58	140	-0.54	0.67	139	12.5%	-0.67 [-0.82, -0.52]	
Wilding 2012 Subtotal (95% CI)	-1.01	0.72	164 383	-0.47	0.77	157 373	11.7% 36.1%	-0.54 [-0.70, -0.38] -0.54 [-0.69, -0.38]	<del>-</del>
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup> = 5	5.93, df = 2	2 (P = 0.	05); I <sup>2</sup> = 66%	0				
Test for overall effect:	Z = 6.78 (P <	0.00001)	`	,-					
Total (95% CI)			1084			1060	100.0%	-0.54 [-0.63, -0.44]	•
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup> = 2	22.81, df =	8 (P = 0	0.004); I <sup>2</sup> = 6	5%			•	1 05 0 05 1
Test for overall effect:	Z = 10.99 (P	< 0.00001	)					Fa	-1 -0.5 0 0.5 1 avours dapagliflozin Favours placebo
Test for subgroup diffe	rences: Chi²	= 0.37, df	= 1 (P =	$0.55$ ), $I^2 = 0$	%			Га	avours dapagiiiloziii i avours piacebo

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). 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). In the RCT of 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).

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

2.1 up to 26 weeks  tailey 2010										
2.1 up to 26 weeks  tailey 2010		Dapaglif	flozin (10	mg)	PI	acebo	)		Mean Difference	Mean Difference
Tailey 2010  -2.9	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	IV, Random, 95% CI
tolinder 2012	1.2.1 up to 26 weeks									
Rosenstock 2012 -0.14 2.3 140 1.64 2.3 139 14.8% -1.78 [-2.32, -1.24] -1.5trojek 2011 -2.26 1.5 151 -0.72 1.47 145 27.8% -1.54 [-1.88, -1.20] -1.5trojek 2011 -2.26 1.5 151 -0.72 1.47 145 27.8% -1.54 [-1.88, -1.20] -1.5trojek 2011 -2.26 1.5 151 -0.72 1.47 145 27.8% -1.54 [-1.88, -1.20] -1.5trojek 2012 -1.61 2.51 177 0.43 2.51 168 15.2% -2.04 [-2.57, -1.51] -1.5tropek 2012 -1.61 2.51 177 0.43 2.51 168 15.2% -2.04 [-2.57, -1.51] -1.81 [-2.04, -1.57]	Bailey 2010	-2.9	2.62	133	-0.9	2.95	136	10.5%	-2.00 [-2.67, -1.33]	<del></del>
Attrojek 2011 -2.26 1.5 151 -0.72 1.47 145 27.8% -1.54 [-1.88, -1.20] -1.54 [-1.88, -1.20] -1.59 [-1.61 2.51 177 0.43 2.51 168 15.2% -2.04 [-2.57, -1.51] -1.59 [-2.04, -1.57] -1	Bolinder 2012	-2.96	2.61	89	-0.88	2.62	91	8.3%	-2.08 [-2.84, -1.32]	<del></del>
Vilding 2009	Rosenstock 2012	-0.14	2.3	140	1.64	2.3	139	14.8%	-1.78 [-2.32, -1.24]	<del></del>
Vilding 2012 -1.61 2.51 177 0.43 2.51 168 15.2% -2.04 [-2.57, -1.51]    viubtotal (95% CI) 713 701 79.5% -1.81 [-2.04, -1.57]    leterogeneity: Tau² = 0.01; Chi² = 5.30, df = 5 (P = 0.38); I² = 6%   lest for overall effect: Z = 15.17 (P < 0.00001)     2.2.2 48 weeks and more    violinder 2012 -4.39 4.14 81 -2.03 4.03 84 3.4% -2.36 [-3.61, -1.11]    violender 2012 0.69 3 140 2.99 3.4 139 8.5% -2.30 [-3.05, -1.55]    vilding 2012 -1.61 3.48 166 0.82 3.39 157 8.6% -2.43 [-3.18, -1.68]    vibitotal (95% CI) 387 380 20.5% -2.36 [-2.85, -1.88]    leterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); I² = 17%    leterogeneity: Tau² = 0.02; Chi² = 0.00001	Strojek 2011	-2.26	1.5	151	-0.72	1.47	145	27.8%	-1.54 [-1.88, -1.20]	-
Subtotal (95% CI)  713  701  79.5%  -1.81 [-2.04, -1.57]  • leterogeneity: Tau² = 0.01; Chi² = 5.30, df = 5 (P = 0.38); I² = 6%  rest for overall effect: Z = 15.17 (P < 0.00001)  2.2.48 weeks and more  rollinder 2012  -4.39  4.14  81  -2.03  4.03  84  3.4%  -2.36 [-3.61, -1.11]  rosenstock 2012  0.69  3  140  2.99  3.4  139  8.5%  -2.30 [-3.05, -1.55]	Wilding 2009	-4.5	2.31	23	-1.9	2.26	22	3.0%	-2.60 [-3.94, -1.26]	· · · · · ·
leterogeneity: Tau² = 0.01; Chi² = 5.30, df = 5 (P = 0.38); I² = 6% lest for overall effect: Z = 15.17 (P < 0.00001)  2.2.48 weeks and more lolinder 2012	Wilding 2012	-1.61	2.51	177	0.43	2.51	168	15.2%	-2.04 [-2.57, -1.51]	- <del>-</del>
est for overall effect: Z = 15.17 (P < 0.00001)  2.2.48 weeks and more  dolinder 2012	Subtotal (95% CI)			713			701	79.5%	-1.81 [-2.04, -1.57]	<b>♦</b>
2.2.2.48 weeks and more  tolinder 2012	Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup> =	= 5.30, df	= 5 (P =	0.38); I	$^{2} = 6\%$	)			
tolinder 2012 -4.39 4.14 81 -2.03 4.03 84 3.4% -2.36 [-3.61, -1.11] Rosenstock 2012 0.69 3 140 2.99 3.4 139 8.5% -2.30 [-3.05, -1.55] Viding 2012 -1.61 3.48 166 0.82 3.39 157 8.6% -2.43 [-3.18, -1.68] Rubtotal (95% CI) 387 380 20.5% -2.36 [-2.85, -1.88] Reterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); l² = 0% Rest for overall effect: Z = 9.49 (P < 0.00001)  Fotal (95% CI) 1100 1081 100.0% -1.95 [-2.18, -1.71] Reterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% Rest for overall effect: Z = 16.17 (P < 0.00001)	Test for overall effect:	Z = 15.17 (F	P < 0.000	01)						
Rosenstock 2012 0.69 3 140 2.99 3.4 139 8.5% -2.30 [-3.05, -1.55]  Vilding 2012 -1.61 3.48 166 0.82 3.39 157 8.6% -2.43 [-3.18, -1.68]  Subtotal (95% CI) 387 380 20.5% -2.36 [-2.85, -1.88]  Very for overall effect: Z = 9.49 (P < 0.00001)  Votal (95% CI) 1100 1081 100.0% -1.95 [-2.18, -1.71]  Votal (95% CI) 100 1081 100.0% -1.95 [-2.18, -1.71]	1.2.2 48 weeks and m	ore								
leterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); l² = 0% leterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); l² = 0% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17%	Bolinder 2012	-4.39	4.14	81	-2.03	4.03	84	3.4%	-2.36 [-3.61, -1.11]	
leterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); l² = 0% leterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); l² = 0% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17%	Rosenstock 2012	0.69	3	140	2.99	3.4	139	8.5%	-2.30 [-3.05, -1.55]	<del></del>
leterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); l² = 0% leterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); l² = 0% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17% leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17%	Wilding 2012	-1.61	3.48	166	0.82	3.39	157	8.6%	-2.43 [-3.18, -1.68]	<del></del>
Test for overall effect: Z = 9.49 (P < 0.00001)  Total (95% CI)  1100  1081  100.0%  -1.95 [-2.18, -1.71]    Interrogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17%    Interrogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17%    Interrogeneity: Tau² = 0.000(1)	Subtotal (95% CI)			387			380	20.5%	-2.36 [-2.85, -1.88]	•
fotal (95% CI) 1100 1081 100.0% -1.95 [-2.18, -1.71]	Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> =	= 0.06, df	= 2 (P =	0.97); I	<sup>2</sup> = 0%	)			
leterogeneity: Tau² = 0.02; Chi² = 9.69, df = 8 (P = 0.29); l² = 17%	Test for overall effect:	Z = 9.49 (P	< 0.0000	1)						
-4 -2 U 2	Total (95% CI)			1100			1081	100.0%	-1.95 [-2.18, -1.71]	<b>•</b>
-4 -2 U 2	Heterogeneity: Tau <sup>2</sup> =	0.02; Chi <sup>2</sup> =	= 9.69, df	= 8 (P =	0.29); I	<sup>2</sup> = 17 <sup>9</sup>	%			<del></del>
	• •			,	,,				,	
est for subgroup differences: Chi <sup>2</sup> = 4.33, df = 1 (P = 0.04), l <sup>2</sup> = 76.9%		'		,	= 0.04	).  2 = 7	76.9%		l	Favours experimental Favours control

## 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).<sup>16</sup>

## 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.<sup>11</sup>

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). <sup>16</sup>

#### **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.<sup>16</sup>

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. <sup>14</sup> 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. <sup>13</sup> 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). <sup>11</sup>

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.<sup>16</sup>

# Other adverse events

Three studies reported deaths in dapagliflozin groups (Bolinder 2011 (one death), Strojek 2011 (two deaths), Wilding 2012 (two deaths)). <sup>9;13;15</sup> 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. <sup>11</sup>

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). 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.

## **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. <sup>17</sup> 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<sup>18</sup>), 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<sup>19</sup>) 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%. <sup>21</sup>

Musso et al. (2012)<sup>21</sup> 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. 47<sup>th</sup> 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. 72<sup>nd</sup> 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

	JL, Pieters A, Bastien A, List JF. <b>Effect of dapa</b> andomised, double-blind, placebo-controlled		who have inadequate glycaemic control with	Funding source: Astra-Zeneca and Bristol-Myers-Squibb
				SGLT2 inhibitor (2.5, 5 or 10 mg dapagliflozin) + metformin versus placebo + metformin
Aim: to determ	ine the efficacy and safety of dapagliflozin in t	ype 2 diabetes in patients with inadequate	HbA1c control with metformin alone	
Study quality	High – see quality table for further informat	ion		
Study	Multi-centre: 80 (USA, Canada, Argentina, I	Mexico, Brazil)		
particulars	Duration of intervention: 24 weeks			
	Duration of run in: 2 weeks			
	Follow-up: on completion of 24 weeks, a 10	2 week long-term study		
	Design: 4-arm parallel-group RCT, double bl	ind, placebo controlled		
	Primary outcome: change from baseline in	HbA1c at week 24		
	Secondary outcomes:			
	At 24 weeks changes in:			
	<ul> <li>Fasting plasma glucose</li> </ul>			
		c <7%, number with HbA1c of 9% or more		
	,	e in bodyweight, and decreases in bodywe	eight of 5% or more	
	<ul> <li>Laboratory tests, adverse events</li> </ul>			
Participant	N: 534 analysed			
criteria	Inclusion criteria: participants aged betwee metformin ≥1500 mg per day	n 18 and 77 years; type 2 diabetes; BMI ≤4	5 kg/m <sup>2</sup> ; HbA1c 7 to 10.0%; fasting C-peptide	e ≥0.34 ng/ml; taking stable dose
	, , , , , , , , , , , , , , , , , , ,	mol/L for men or >124 umol/L for women (	consistent with metformin labelling); urine a	Ihumin/creatinine ratio >203 4 mg/mmol
			oper limit of normal, symptoms of poorly con	
		•	; systolic blood pressure ≥180 mmHg or diast	·
	significant other systemic disease	, , , , , , , , , , , , , , , , , , ,	, , , , , , , , , , , , , , , , , , , ,	3, 1
Interventions	Intervention 1: 2.5 mg dapagliflozin + metfo	ormin		
	Intervention 2: 5 mg dapagliflozin + metfor			
	Intervention 3: 10 mg dapagliflozin + metfo			
	Intervention 4: matching placebo + metform	nin		
	OAD schedule: metformin at pre-study dose	e (≥1500 mg/day; mean dose 1792 to 1861	mg/day); dapagliflozin once daily before mo	rning meal
	All groups: diet and exercise counselling			
	Lead in period: 2 weeks, single blind, to ass	sess compliance with placebo, patients ran	domised after successful completion; metfor	min dose (open label 500 mg tablets)
	continued at pre-study levels			
Participant	Group 1 (n analysed=134):	Group 2 (n=135):	Group 3 (n=133):	Group 4 (n=132):
baseline data	Placebo OD + metformin	2.5 mg dapagliflozin OD + metformin	5 mg dapagliflozin OD + metformin	10 mg dapagliflozin OD + metformin
	Age: 53.7 SD10.3 years	<b>Age:</b> 55.0 SD9.3 years	<b>Age:</b> 54.3 SD9.4 years	<b>Age:</b> 52.7 SD9.9 years
	<b>Sex:</b> 55% male	Sex: 51% male	Sex: 50% male	<b>Sex:</b> 57% male

	<b>HbA1c (%):</b> 8.11% SD0.96		BMI (kg/m	n²): 31.6 SD4.8	BMI (kg/m²): 31.4 SD5.0		BMI (kg/m²): 31.2 SD5.1		
			HbA1c (%)	: 7.99% SD0.90	HbA1c (%	): 8.17% SD0.96	HbA1c (%): 7.92% SD0.82		
			Duration of	<b>Duration of diabetes:</b> 6.0 SD6.2 years		of diabetes: 6.4 SD5.8 years	Duration of	liabetes: 6.1 SD5.4 years	
	FPG (mmol/L):			ol/L): 8.96 SD2.39		ol/L): 9.39 SD2.72		.): 8.66 SD2.15	
		mHg): 127.7 SD14.6	-	P (mmHg): 126.6 SD14.5	-	P (mmHg): 126.9 SD14.3		nmHg): 126.0 SD15.9	
Outcome (chan	ge from baseline	to study end (week 24))	-					<u> </u>	
-	Group 1 (n=13	4):	Group 2 (n	Group 2 (n=135):		n=133):	Group 4 (n=1	32):	
	Placebo OD +	metformin	2.5 mg dar	pagliflozin OD + metformin	5 mg dapa	agliflozin OD + metformin	10 mg dapag	liflozin 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	
	Major hypogl	ycaemia = symptomatic epis ycaemia = symptomatic epis overy, capillary glucose <3.0n	ode, needing e		>5% UTI = Urin GTI = Gen	events – where frequency is nary Tract Infection ital Tract Infection	At least one or more adverse event Group 1 = n=88 Group 2 = n=89 Group 3 = n=95		
					HypoG = H	łypotension łypoglycaemia	<b>Group 4 =</b> n=	98	
	Group 1 (n an	alysed=134):	Group 2 (n	n= 135):	Group 3 (	n= 133):	Group 4 (n=	132):	
	Placebo OD +	metformin		pagliflozin OD + metformin		agliflozin OD + metformin		10 mg dapagliflozin OD + metformin	
Specific events	UTI n=11, GTI	n=7	UTI n= 6, G	GTI n=11	UTI n=10,	GTI n=18	UTI n=16, GT	l n=12	
	HypoT n=1, Hy		HypoT n=0	), HypoG n=3	HypoT n=	2, HypoG n=5	HypoT n=0, F	lypoG n=5	
	Events leading	g to discontinuation n=5	Events lead	ding to discontinuation n=3	Events lea	ading to discontinuation n=3	Events leadin	g to discontinuation n=4	
	Diarrhoea n=7	7	Diarrhoea	n=3	Diarrhoea	ı n=5	Diarrhoea n=	10	
	Back pain n=7		Back pain i	n=5	Back pain	n=3	Back pain n=	10	
	Nasopharyngi	tis n=11		ngitis n=12/		yngitis n=4	Nasopharyng	itis n=8	
	Cough n=7		Cough n=4		Cough n=		Cough n=1		
	Influenza n=10	0	Influenza r	n=13	Influenza	n=13	Influenza n=8	3	
	Hypertension	n=6	Hypertens	ion n=9	Hypertens	sion n=4	Hypertension	n n=5	
		act Infection n=10		o. tract Infection n=5		p. tract Infection n=4		ract Infection n=3	
	Headache n=6	5	Headache	Headache n=4		Headache n=1		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, Funding source: Astra-Zeneca and and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. Journal of Bristol-Myers-Squibb Clinical Endocrinology and Metabolism 2012; 97(3): 1020-10319 SGLT2 inhibitor (10 mg dapagliflozin) + metformin Ljunggren Ö, Bolinder J, Johansson L, Langkilde AM, Sjöström CD, Sugg J, Parikh S. Dapagliflozin has no effect on markers of bone formation and versus placebo + metformin 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]<sup>10</sup> 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** N: 180 analysed criteria 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<sup>2</sup>; 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

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

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

Group 1 (start n= 91,	Group 2 (start n=	Group 2 (start n= 91, analysed n= 89): 10 mg dapagliflozin + metformin				
Age: 60.8 SD6.9 years		Age: 60.6 SD8.2 y	vears			
Sex: 56% male						
BMI (kg/m²): 31.7 SD3	3.9	BMI (kg/m²): 32.	1 SD3.9			
HbA1c (%): 7.16% SDC	1.53	HbA1c (%): 7.199	6 SD0.44			
				ars		
	· · · · · · · · · · · · · · · · · · ·		•			
from baseline to study e	nd (24 weeks))					
Group 1 (n=91): Place	bo + metformin	Group 2 (n= 89):	10 mg dapagliflozi	n + metformin		
Mean	95% CI	Mean	95% CI			
-0.10	-0.01 to -0.19 [from graph]	-0.39	-0.29 to -0.	49 [from graph], p<0.0001 vs placebo		
-0.88	-1.43 to -0.34	-2.96		41, p<0.0001 vs placebo		
+0.13	NR			01 vs placebo		
	SD		SD			
			NR			
		•	•			
ns		, ,				
		General events -	where	At least one or more adverse event		
<3.5mmol/L, asympto	matic episode with glucose <3.5 mmol/L	frequency is >2%	frequency is >2%  UTI = Urinary Tract Infection  GTI = Genital Tract Infection  GTI = Genital Tract Infection			
assistance with capilla	ry glucose <3.0mmol/L, recovery following glucose o	GTI = Genital Tra				
glucagon administration	on	HypoS = Hypogly	caemia (severe)	1 death in dapagliflozin group, no deaths in		
Other hypoglycaemia	(HypoO) = symptoms, but without confirmative	HypoM = Hypogh	/caemia (mild)	placebo group		
measurement		HypoO = Hypogly	caemia other			
		HypoT = Hypoter	sion	No significant effect on bone formation and		
				resorption or bone mineral density		
Group 1 (n=91): Place	bo + metformin	Group 2 (n= 89):	10 mg dapagliflozi	n + metformin		
UTI n=2, GTI n=0		UTI n=6, GTI n=3				
HypoM n=2, HypoS n=	0, HypoO n=1	HypoM n=2, Hyp	oS n=0, HypoO n=0	)		
HypoT n=0		HypoT n=1				
Events leading to disco	ontinuation n=0	Events leading to	Events leading to discontinuation n=5			
Nasopharyngitis n=5		Nasopharyngitis	Nasopharyngitis n=6			
Hypertension n=4		Hypertension n=4	Hypertension n=4			
Pneumonia n=0		Pneumonia n=3	7.1			
	1	Angina pectoris n=2				
Angina pectoris n=0		Angina pectoris r	9 ,			
Angina pectoris n=0 Cystitis n=1		Angina pectoris r Cystitis n=2				
Cystitis n=1		Cystitis n=2				
ıt	Age: 60.8 SD6.9 years Sex: 56% male BMI (kg/m²): 31.7 SD3 HbA1c (%): 7.16% SD0 Duration of diabetes: FPG (mmol/L): 8.3 SD: from baseline to study er Group 1 (n=91): Place Mean -0.10 -0.88 +0.13 Mean 0.1  t: assessed via adverse events  Minor hypoglycaemia <3.5mmol/L, asympto Severe hypoglycaemia assistance with capilla glucagon administratic Other hypoglycaemia measurement  Group 1 (n=91): Place UTI n=2, GTI n=0 HypoM n=2, HypoS n= HypoT n=0 Events leading to disco	BMI (kg/m²): 31.7 SD3.9 HbA1c (%): 7.16% SD0.53 Duration of diabetes: 5.5 SD5.3 years FPG (mmol/L): 8.3 SD1.4 from baseline to study end (24 weeks))  Group 1 (n=91): Placebo + metformin  Mean 95% CI -0.10 -0.01 to -0.19 [from graph] -0.88 -1.43 to -0.34 +0.13 NR Mean SD 0.1  NR  Mean SD 0.1  Minor hypoglycaemia (HypoM) = symptomatic episode, capillary glucose <3.5 mmol/L, asymptomatic episode with glucose <3.5 mmol/L Severe hypoglycaemia (HypoS) = symptomatic episode needing external assistance with capillary glucose <3.0 mmol/L, recovery following glucose or glucagon administration Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement  Group 1 (n=91): Placebo + metformin  UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO n=1 HypoT n=0 Events leading to discontinuation n=0 Nasopharyngitis n=5 Hypertension n=4	Age: 60.8 SD6.9 years Sex: 56% male BMI (kg/m²): 31.7 SD3.9 HbA1c (%): 7.16% SD0.53 Duration of diabetes: 5.5 SD5.3 years FPG (mmol/L): 8.3 SD1.4 FPG (mmol/L): 8.3 SD1.4 FPG (mmol/L): 8.3 SD1.4 FPG (mmol/L): 8.3 SD1.4  Group 1 (n=91): Placebo + metformin  Mean 95% CI Mean -0.10 -0.01 to -0.19 [from graph] -0.39 -0.88 -1.43 to -0.34 -2.96 +0.13 NR -0.82 Mean  0.1 NR -2.7  Age: 60.6 SD8.2 y Sex: 55.1% male BMI (kg/m²): 32. HbA1c (%): 7.19% Duration of diabetes: 5.5 SD5.3 years FPG (mmol/L): 8.3 SD1.4  FPG (mmol/L): 8.3 FPG (mmol/L): 8.3 SD1.4  Mean -0.10 -0.10 -0.01 to -0.19 [from graph] -0.39 -0.88 -1.43 to -0.34 -2.96 -0.13 NR -2.96 -0.13 NR -2.77  Age: 60.6 SD8.2 y Sex: 55.1% male BMI (kg/m²): 32. Mean -1.43 to -0.34 -1.43 to -0.39 -1.43 to -0.3	Age: 60.8 SD6.9 years Sex: 55.% male BMI (kg/m²): 31.7 SD3.9 HbA1c (%): 7.16% SD0.53 Duration of diabetes: 5.5 SD5.3 years FPG (mmol/L): 8.2 SD1.4  from baseline to study end (24 weeks))  Group 1 (n=91): Placebo + metformin Mean 95% Cl 40.10 -0.10 -0.01 to -0.19 [from graph] -0.39 -0.29 to -0.39 -0.29 to -0.4 -0.13 NR -0.82 NR, p<0.00 Mean SD 0.1 NR  t: assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionna strange assistance with capillary glucose < 3.5 mmol/L, asymptomatic episode with glucose or glucagon administration Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement  Win p 1 (n=91): Placebo + metformin Group 2 (n=89): 10 mg dapagliflozi Mean 95% Cl NR -0.39 -0.29 to -00.39 -0.29 to -00.98 NR -0.82 NR, p<0.00 Mean SD  0.1 NR  Unimary productions (MedDRA v12.1) via patient questionna strange assistance with capillary glucose < 3.5 mmol/L Severe hypoglycaemia (HypoM) = symptomatic episode, capillary glucose or glucagon administration Other hypoglycaemia (HypoS) = symptomatic episode needing external assistance with capillary glucose <3.0 mmol/L, recovery following glucose or glucagon administration Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement  Group 1 (n=91): Placebo + metformin  Group 2 (n=89): 10 mg dapagliflozi UTI n=2, GT n=0 HypoM n=2, HypoS n=0, HypoO n=0 HypoM n=2, HypoS n=0, HypoS n=0, HypoO n=0 HypoT n=0 Events leading to discontinuation n=0 Nasopharyngitis n=5 Hypertension n=4		

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Type E diabetes will	o have inadequate glycaemic control with metformin. Diabetes Care 2011; 34: 20	15-2022 <sup>11</sup>	Bristol-Myers-Squibb			
			SGLT2 inhibitor (up to 10 mg dapagliflozin) + metformin versus metformin + glipizide			
Aim: to compare the	e efficacy, safety and tolerability of dapagliflozin with glipizide in patients with typ	e 2 diabetes inadequately controlled with monot	herapy			
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	N: 801 analysed		_			
criteria	Inclusion criteria: participants aged 18 years and older; inadequately controlled type 2 diabetes (HbA1c >6.5 and ≤10%); BMI ≤45kg/m²; fasting C-peptide ≥0.33 nmol/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					
Interventions	normal; total bilirubin >34 μmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL					
Interventions	normal; total bilirubin >34 μmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose 9.2 mg/day)					
Interventions	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200	for women; abnormal TSH; systolic blood pressu  0 mg/day); dapagliflozin started at 2.5 mg, up-ti	ure ≥180 mmHg and/or diastolic blood			
Interventions	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up-	for women; abnormal TSH; systolic blood pressu  0 mg/day); dapagliflozin started at 2.5 mg, up-ti	ure ≥180 mmHg and/or diastolic blood			
Interventions	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up all groups: diet and lifestyle advice	for women; abnormal TSH; systolic blood pressu 0 mg/day); dapagliflozin started at 2.5 mg, up-ti o 20 mg)	are ≥180 mmHg and/or diastolic blood			
	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformin stabilised to	for women; abnormal TSH; systolic blood pressu 0 mg/day); dapagliflozin started at 2.5 mg, up-ti o 20 mg) 1500 to 2000 mg/day; 2 weeks single blind place	are ≥180 mmHg and/or diastolic blood			
Participant	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up-All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformin stabilised to Group 1 (start n= 406, analysed n=400):	for women; abnormal TSH; systolic blood pressure of mg/day); dapagliflozin started at 2.5 mg, up-tion 20 mg)  1500 to 2000 mg/day; 2 weeks single blind place of Group 2 (start n= 408, analysed n= 401):	are ≥180 mmHg and/or diastolic blood			
	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up-All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformin stabilised to Group 1 (start n= 406, analysed n=400):  9.2 mg dapagliflozin + metformin	for women; abnormal TSH; systolic blood pressure of mg/day); dapagliflozin started at 2.5 mg, up-tion 20 mg)  1500 to 2000 mg/day; 2 weeks single blind place of Group 2 (start n= 408, analysed n= 401): 16.4 mg glipizide + metformin	are ≥180 mmHg and/or diastolic blood			
Participant	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up-All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformin stabilised to Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years	for women; abnormal TSH; systolic blood pressure of mg/day); dapagliflozin started at 2.5 mg, up-tion 20 mg)  1500 to 2000 mg/day; 2 weeks single blind place of the main of t	are ≥180 mmHg and/or diastolic blood			
Participant	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up-All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformin stabilised to Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years Sex: 55.3% male	for women; abnormal TSH; systolic blood pressure of the property of the proper	are ≥180 mmHg and/or diastolic blood			
Participant	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformin stabilised to Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years  Sex: 55.3% male  BMI (kg/m²): 31.7 SD5.1	for women; abnormal TSH; systolic blood pressure of mg/day); dapagliflozin started at 2.5 mg, up-tion 20 mg)  1500 to 2000 mg/day; 2 weeks single blind place of many started at 2.5 mg, up-tion 20 mg)  1500 to 2000 mg/day; 2 weeks single blind place of many started at 2.5 mg, up-tion 20 mg/day; 2 weeks single blind place of many started at 2.5 mg, up-tion 20 mg/day; 2 weeks single blind place of many started at 2.5 mg, up-tion 20 mg/day); analysed n= 401):  16.4 mg glipizide + metformin  Age: 59 SD10 years  Sex: 54.9% male  BMI (kg/m²): 31.2 SD5.1	are ≥180 mmHg and/or diastolic blood			
Participant	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformin stabilised to Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years  Sex: 55.3% male  BMI (kg/m²): 31.7 SD5.1  ≥ 25 kg/m²: 95%	for women; abnormal TSH; systolic blood pressure of the proof of the	are ≥180 mmHg and/or diastolic blood			
Participant	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (upragous)  All groups: diet and lifestyle advice Lead in period: before lead in: other OADs discontinued, metformin stabilised to Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years  Sex: 55.3% male  BMI (kg/m²): 31.7 SD5.1  ≥ 25 kg/m²: 95%  ≥ 30 kg/m²: 57%	for women; abnormal TSH; systolic blood pressure  0 mg/day); dapagliflozin started at 2.5 mg, up-tion 20 mg)  1500 to 2000 mg/day; 2 weeks single blind place  Group 2 (start n= 408, analysed n= 401): 16.4 mg glipizide + metformin  Age: 59 SD10 years Sex: 54.9% male BMI (kg/m²): 31.2 SD5.1  ≥ 25 kg/m²: 90.8%  ≥ 30 kg/m²: 55.4%	are ≥180 mmHg and/or diastolic blood			
Participant	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up of All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformin stabilised to Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years  Sex: 55.3% male  BMI (kg/m²): 31.7 SD5.1  ≥ 25 kg/m²: 95%  ≥ 30 kg/m²: 57%  HbA1c (%): 7.7% SD0.9	for women; abnormal TSH; systolic blood pressure  0 mg/day); dapagliflozin started at 2.5 mg, up-tion 20 mg)  1500 to 2000 mg/day; 2 weeks single blind place  Group 2 (start n= 408, analysed n= 401): 16.4 mg glipizide + metformin  Age: 59 SD10 years Sex: 54.9% male BMI (kg/m²): 31.2 SD5.1  ≥ 25 kg/m²: 90.8%  ≥ 30 kg/m²: 55.4%  HbA1c (%): 7.7% SD0.9	are ≥180 mmHg and/or diastolic blood trated to maximum tolerable dose (up			
Participant	normal; total bilirubin >34 µmol/L; haemoglobin ≤11 g/dL for men and ≤10 g/dL pressure ≥110 mmHg; significant other disease  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 200 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (upragous)  All groups: diet and lifestyle advice Lead in period: before lead in: other OADs discontinued, metformin stabilised to Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years  Sex: 55.3% male  BMI (kg/m²): 31.7 SD5.1  ≥ 25 kg/m²: 95%  ≥ 30 kg/m²: 57%	for women; abnormal TSH; systolic blood pressure  0 mg/day); dapagliflozin started at 2.5 mg, up-tion 20 mg)  1500 to 2000 mg/day; 2 weeks single blind place  Group 2 (start n= 408, analysed n= 401): 16.4 mg glipizide + metformin  Age: 59 SD10 years Sex: 54.9% male BMI (kg/m²): 31.2 SD5.1  ≥ 25 kg/m²: 90.8%  ≥ 30 kg/m²: 55.4%	are ≥180 mmHg and/or diastolic blood trated to maximum tolerable dose (up			

	Group 1 (n=400): 9.2 mg c	lapagliflozin + metformin	Group 2 (n= 401): 16.4 mg glipizide + m	etformin		
	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 Activitie	s (MedDRA v12.1) via patient questionnaire a	nd active questioning during visits		
	assistance with following I Minor hypoglycaemia (Hy <3.5mmol/L	ypoS) = symptomatic episode, needing external ecovery, capillary glucose <3.0mmol/L poM) = symptomatic episode, capillary glucose poO) = symptoms, but without measurement	General events – where frequency is ≥3%  UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe)	At least one or more adverse event Group 1 = n=318 Group 2 = n=318  No deaths in dapagliflozin group		
	confirming	760	HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia other HypoT = Hypotension	3 deaths in glipizide group		
	Group 1 (n=406): 9.2 mg c	lapagiifiozin + metformin	Group 2 (n= 408): 16.4 mg glipizide + m	ettormin		
Specific events	UTI n=44, GTI n=50 HypoS n=0, HypoM n=7, H HypoT n=6 Renal impairment / failure Events leading to discontin		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	71 07	Diarrhoea n=26			
	Nausea n=14		Nausea n=15			
	Vulvovaginal mycotic infe	ction n=14	Vulvovaginal mycotic infection n=2			
	Back pain n=19		Back pain n=20			
	Nasopharyngitis n= 43		Nasopharyngitis n=61			
	Cough n=15		Cough n=20	Cough n=20		
	Influenza n=30		Influenza n=30			
	Arthralgia n=11		Arthralgia n=21			
	Upper resp. tract Infection	n n=24	Upper resp. tract Infection n=31	Upper resp. tract Infection n=31		
	Headache n=21		Headache n=17			
	Hypertension n=30		Hypertension n=35			

	M, Wei L, Salsali A, List JF. <b>Effects of dapagliflozin, an S</b> <b>2 diabetes inadequately controlled in pioglitazone me</b>	GLT2 inhibitor, on HbA1c, body weight, and hypoglycaemia onotherapy. Diabetes Care 2012; 35: 1473-1478 <sup>12</sup>	Funding source: Astra-Zeneca and Bristol-Myers-Squibb					
			SGLT2 inhibitor (5 or 10 mg dapagliflozin) + pioglitazone versus placebo + pioglitazone					
Aim: to examine the	e safety and efficacy of dapagliflozin added to pioglita	cone in type 2 diabetes patients inadequately controlled on p	pioglitazone					
Study quality	Low – see quality table for further information							
Study particulars	Multi-centre: 105 (Argentina, Canada, India, Mexico	o, 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, place	ebo controlled						
	Primary outcome: change from baseline in HbA1c a	t 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	N: 420 analysed							
criteria	Inclusion criteria: participants with type 2 diabetes; age ≥18 years; fasting C-peptide ≥1.0 ng/mL; BMI ≤45 kg/m²; 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, conges	tive 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							
	<b>Lead in period:</b> 2 weeks, single blind, placebo lead	n						
Participant	Group 1 (n=139): Placebo + pioglitazone	Group 2 (n=141): 5 mg dapagliflozin + pioglitazone	Group 2 (n=140): 10 mg dapagliflozin + pioglitazone					
baseline data	<b>Age:</b> 53.5 SD11.4 years	<b>Age:</b> 53.2 SD10.9 years	<b>Age:</b> 53.8 SD10.2 years					
	<b>Sex:</b> 51.1% male	<b>Sex:</b> 55.3% male	<b>Sex:</b> 42.1% male					
	<b>BMI:</b> $61.2\% \ge 30 \text{ kg/m}^2$ ; $87.8\% \ge 25 \text{ kg/m}^2$	<b>BMI:</b> $61.7\% \ge 30 \text{ kg/m}^2$ ; $86.5\% \ge 25 \text{ kg/m}^2$	<b>BMI:</b> $51.4\% \ge 30 \text{ kg/m}^2$ ; $92.9\% \ge 25 \text{ kg/m}^2$					
	<b>HbA1c:</b> 8.34% SD1.00	<b>HbA1c:</b> 8.40% SD1.03	<b>HbA1c:</b> 8.37% SD0.96					
	Duration of diabetes: 5.07 SD5.05 years	<b>Duration of diabetes:</b> 5.64 SD5.36 years	<b>Duration of diabetes:</b> 5.75 SD6.44 years					

	FPG (mmol/L): 8.92 S		FPG (mmol/L): 9.36 SE	02.89	<b>FPG (mmol/L):</b> 9.15 SD2.57				
Outcome (change	from baseline to study e	end)							
	Group 1 (n=139): Placebo + pioglitazone Group 2 (n=141): 5		Group 2 (n=141): 5 mg	ng dapagliflozin + pioglitazone		up 2 (n=140):	10 mg dapagliflozin + pioglitazon		
	Mean	SE	Mean		Mean		SE		
ΔHbA1c (%)	wk 24: -0.42	0.08	-0.82	0.08, p=0.0007 vs placebo	-0.9	7	0.08, p<0.0001 vs placebo		
	wk 48: -0.54	0.08	-0.95	0.08, p NR	-1.2	1	0.07, p NR		
ΔWeight (kg)	wk 24: +1.64	0.28	+0.09	0.28, p<0.0001 vs placebo	-0.1	4	0.28, p<0.0001 vs placebo		
	wk 48: +2.99	0.41	+1.35	0.38, p NR	+0.6	9	0.36, p NR		
ΔFPG (mmol/L)	wk 24: -0.31	0.16	-1.38	0.16, p<0.0001 vs placebo	-1.6	1	0.16, p<0.0001 vs placebo		
	wk 48: -0.73	0.20	-1.27	0.18, p NR	-1.8	4	0.17, p NR		
ΔSBP (mmHg)	wk 24: +1.3	1.2	-0.8	1.2, p NS	-3.4		1.2, p NS		
	wk 48: +2.0	1.2	-1.0	1.1, p NR	-2.2		0.7, p NR		
Adverse events			<u>.</u>						
Safety assessment	: assessed at every visit,	questioning, laboratory tes	sts and vital signs						
•		a (HypoM) = symptomatic e		General events – where		At least one	e or more adverse event		
	<3.5mmol/L, asympto	omatic episode with glucose	e <3.5 mmol/L	de needing external  ry following glucose or  GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe		<b>Group 1 = 6</b>	66.9%		
	Severe hypoglycaem	ia (HypoS) = symptomatic e	episode needing external			Group 2 = 68.1% Group 3 = 70.7%			
	assistance with capilla	ary glucose <3.0mmol/L, re	covery following glucose or						
	glucagon administrat	ion							
	Other hypoglycaemia	(HypoO) = symptoms, but	without confirmative						
	measurement			HypoO = Hypoglycaemia othe		er e			
	Group 1 (n=139): Place	cebo + pioglitazone	Group 2 (n=141): 5 mg	g dapagliflozin + pioglitazone	Gro	up 2 (n=140):	10 mg dapagliflozin + pioglitazor		
Specific events	UTI n=11, GTI n=4		UTI n=12, GTI n=13	UTI n=12, GTI n=13		UTI n=7, GTI n=12			
•	Any hypoglycaemia n	=1, HypoS n=0	Any hypoglycaemia n=	Any hypoglycaemia n=3, HypoS n=0		Any hypoglycaemia n=0, HypoS n=0			
	Decreased renal func	tion n=1	Decreased renal funct	Decreased renal function n=2		Decreased renal function n=2			
	Events leading to disc	continuation n=5	Events leading to disco	Events leading to discontinuation n=5		Events leading to discontinuation n=3			
	Dyslipidaemia n=9		Dyslipidaemia n=11		Dyslipidaemia n=16				
	Nasopharyngitis n=7		Nasopharyngitis n=7		Nasopharyngitis n=11				
	Diarrhoea n=6		Diarrhoea n=5		Diar	rhoea n=9			
	Back pain n=4		Back pain n=5	Back pain n=5		Back pain n=8			
	Upper resp. tract infe	ection n=10	Upper resp. tract infec	tion n=10	Upper resp. tract infection n=7				
	Headache n=10		Headache n=3		Hea	dache n=4			
	Pain in extremity n=1		Pain in extremity n=10	1	Pain	in extremity	n=4		
	Oedema peripheral n	=9	Oedema peripheral n=	,			Oedema peripheral n=3		

		th S. <b>Effect of Dapagliflozin in patients with typ</b> le-blind, placebo-controlled trial. Diabetes, Ob						
				SGLT2 Inhibitor (2.5, 5, or 10 mg dapagliflozin)plus glimepiride versus placebo plus glimepiride				
		dapagliflozin treatment, as an add-on therapy	to glimepiride, in patients with inadequately o	controlled type 2 diabetes who had bee				
	lphonylurea monotherapy							
Study quality	High – see quality table for further info							
Study	Multi-centre: 84 sites across 7 countri	es world-wide						
particulars	<b>Duration of intervention</b> : 24 weeks							
	<b>Duration of run in</b> : 1 week for patient	· ·						
	Follow-up: on completion of 24 weeks							
	Design: 4-arm parallel group RCT, dou							
	Primary outcome: change in HbA1c fr	om 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 hady weight from baseline in patients with RMI >27kg/m²							
	Change in total body weight from baseline in patients with BMI ≥27kg/m <sup>2</sup>							
	- Change in FPG							
Participant criteria	N: 592 analysed	B years and older; inadequately controlled type	2 diabatas (UbA1s >7 to <10 0%): BMI <4Ekg	/m²: on stable sulphonylures dose (at				
criteria		or at least 8 weeks prior to enrolment); fasting		in ; on stable sulphonylurea dose (at				
				mol: AST and/or ALT and/or creating				
	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	pregnancy of factation, use of weight loss med	dication within 30 days					
interventions	Intervention 2: 2.5 mg/day dapagliflor	zin + glimeniride						
	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/m² 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							
	Group 1 (n= 146)	Group 2 (n= 154)	Group 3 (n= 145)	Group 4 (n= 151)				
Participant			5 mg dapagliflozin + glimepiride	10 mg dapagliflozin + glimepiride				
•	, , ,	2.5 mg dapagiifiozin + gilmepiride	Jilig dapagiiiloziii + giililepiilde	10 mg dapagiiiloziii + giiillepiilde				
•	Placebo + glimepiride	2.5 mg dapagliflozin + glimepiride <b>Age:</b> 59.9 SD10.14 years	5 . 5					
Participant baseline data	, , ,	Age: 59.9 SD10.14 years Sex: 50% male	Age: 60.2 SD 9.73 years Sex: 50% male	Age: 58.9 SD 8.32 years Sex: 43.7% male				

	kg/m <sup>2</sup> HbA1c: 8.11% SD0.75 HbA1c: 8.12% SD0.78		2% SD0.78	<b>HbA1c:</b> 8.07% SD0.79					
	HbA1c: 8.15	% SD0.74	4 Duration of diabetes: 7.7 SD6.0 years Duration of diabetes: 7.4 SD5.7 years Du		Duration of	<b>Duration of diabetes:</b> 7.2 SD5.5 years			
	Duration of	diabetes: 7.4 SD5.7 years	FPG (mmol	<b>/L):</b> 9.56 SD2.13	FPG (mmol	<b>/L):</b> 9.68 SD2.12	FPG (mmd	FPG (mmol/L): 9.55 SD2.04	
	FPG (mmol/	<b>L):</b> 9.58 SD2.07	Systolic BP	(mmHg): 134.6	Systolic BP	(mmHg): 130.9	Systolic BI	P (mmHg): 132.4	
	Systolic BP	mmHg): 133.3							
Outcome (change	ge from baseli	ne to study end (week 24))							
	Group 1 (n=	146)	Group 2 (n=	= 154)	Group 3 (n=	= 145)	Group 4 (r	n= 151)	
	Placebo + gl	imepiride	2.5 mg dapa	5 mg dapagliflozin + glimepiride 5 mg dapagliflozin + glimepiride		liflozin + glimepiride	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],	-0.63	-0.76 to -0.5 [from graph],	-0.82	-0.94 to -0.7 [from graph],	
				p<0.0001 vs placebo		p<0.0001 vs placebo		p<0.0001 vs placebo	
ΔWeight (kg)	-0.72	-0.96 to -0.48 [from	-1.18	-1.42 to -0.94 [from graph],	-1.56	-1.8 to -1.32 [from graph],	-2.26	-2.5 to -2.02 [from graph],	
		graph]		NS		p<0.0091 vs placebo		p<0.0001 vs placebo	
ΔFPG	-0.11	-	-0.93	-	-1.18	-	-1.58	-	
(mmol/L)									
	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 Activities (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	At least one or more adverse event
			≥3% in any group	<b>Group 1 =</b> n=69; <b>Group 2 =</b> n=80
			UTI = Urinary Tract Infection	<b>Group 3 =</b> n=70; <b>Group 4 =</b> n=76
			GTI = Genital Tract Infection	
			Hypo = Hypoglycaemia	1 death in dapagliflozin 2.5 mg
				1 death in dapagliflozin 10 mg
	Group 1 (n= 146)	Group 2 (n= 154)	Group 3 (n= 145)	Group 4 (n= 151)
	Placebo + glimepiride	2.5 mg dapagliflozin + glimepiride	5 mg dapagliflozin + glimepiride	10 mg dapagliflozin + glimepiride
Specific events	UTI n=9, GTI n= 1	UTI n=6, GTI n=6	UTI n=10, GTI n=9	UTI n=8, GTI n=10
	≥ 1 Hypo n=7	≥ 1 Hypo n=11	≥ 1 Hypo n=10	≥ 1 Hypo n=12
	Renal impairment / failure n=2	Renal impairment / failure n=1	Renal impairment / failure n=1	Renal impairment / failure n=0
	Events leading to discontinuation n=3	Events leading to discontinuation n=5	Events leading to discontinuation n=5	Events leading to discontinuation n=4
	Bronchitis n=1	Bronchitis n=2	Bronchitis n=3	Bronchitis n=5
	Diarrhoea n=5	Diarrhoea n=4	Diarrhoea n=2	Diarrhoea n=0
	Back pain n= 4	Back pain n=3	Back pain n=3	Back pain n=7
	Nasopharyngitis n=4	Nasopharyngitis n=3	Nasopharyngitis n=8	Nasopharyngitis n=5
	Arthralgia n=4	Arthralgia n=6	Arthralgia n=0	Arthralgia n=1
	Upper resp. tract Infection n=4	Upper resp. tract Infection n=5	Upper resp. tract Infection n=6	Upper resp. tract Infection n=7
	Hypertension n=6	Hypertension n=8	Hypertension n=2	Hypertension n=2

insulin plus insulin	ood P, T'joen C, Bastien A, List JF, Fiedorek FT. <b>A study of dapagliflozin in patients with type 2 diabetes receiving high doses of sensitizers. Applicability of a novel insulin-independent treatment.</b> Diabetes Care 2009; 32(9): 1656-1662 <sup>14</sup>	Funding source: Astra-Zeneca and Bristol-Myers-Squibb SGLT2 Inhibitor (10 or 20 mg dapagliflozin) + insulin + OAD versus placebo + insulin + OAD				
Aim: to determine i	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	N: 71 analysed					
criteria	Inclusion criteria: participants aged between 18 and 75 years; type 2 diabetes; BMI ≤45 kg/m²; 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					
	continued at pre-study dose (metformin ≥1000 mg and/or pioglitazone ≥30 mg or rosiglitazone 4 mg (66.7 to 79.2% metformin or	nly, 8.3 to 25% metformin + TZD, 4.3 t				
	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	Group 1 (n=23): Placebo	+ OAD + insulin			Group 3 (n= 24): 2	0 mg dapagliflozin + OAD + insulin	
baseline data	Age: 58.4 SD6.5 years		Age: 55.7 SD9.2 yea	Age: 55.7 SD9.2 years		<b>Age:</b> 56.1 SD10.6 years	
	<b>Sex:</b> 69.6% male		<b>Sex:</b> 54.2% male		<b>Sex:</b> 54.2% male		
	BMI (kg/m <sup>2</sup> ): 34.8 SD4.6	j	BMI (kg/m <sup>2</sup> ): 35.5 S	D3.6	BMI (kg/m²): 36.2	SD4.6	
	HbA1c: 8.40% SD0.9		<b>HbA1c:</b> 8.4% SD0.7		HbA1c: 8.5% SD0.	9	
	Duration of diabetes: 13	3.8 SD 7.3 years	<b>Duration of diabete</b>	s: 11.8 SD5.8 years	Duration of diabe	tes: 11.3 SD5.6 years	
	FPG (mmol/L): 9.22 SD 2	2.86	FPG (mmol/L): 8.67	SD 2.17	FPG (mmol/L): 8.9	98 SD 3.06	
	Systolic BP (mmHg): NR		Systolic BP (mmHg)	: NR	Systolic BP (mmH	g): 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): 2	0 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 adver	rse events, vital signs, laborato	ory measurements				
	Minor hypoglycaemia =	symptomatic episode,	General events - w	General events – where frequency is >5%		ore adverse event	
	capillary glucose <3.5mm	nol/L	UTI = Urinary Tract I	nfection	<b>Group 1 =</b> n=15		
	Major hypoglycaemia =	symptomatic episode,	GTI = Genital Tract Infection HypoT = Hypotension, HypoG = Hypoglycaemia		Group 2 = n=18 Group 3 = n=16		
	needing external assistar	nce with following recovery,					
	capillary glucose <3.0mm		HypoS = major hypo				
	Group 1 (n=23): Placebo	+ OAD + insulin	Group 2 (n= 24): 10	mg dapagliflozin + OAD + insulin		0 mg dapagliflozin + OAD + insulin	
Specific events	UTI n=0, GTI n = 1		UTI n= 0, GTI n = 0		UTI n= 1, GTI n = 5		
	HypoT n=NR, HypoG n=3	3, HypoS n=1	HypoT n=NR, HypoG	T n=NR, HypoG n=7, HypoS n=0		oG n=6, HypoS n=0	
	Events leading to discont	tinuation n=1	Events leading to dis	scontinuation n=1	Events leading to d	discontinuation n=1	
	Nausea n=1		Nausea n=1		Nausea n=3 Pollakiuria n=3		
	Pollakiuria n=4		Pollakiuria n=2				
	Back pain n=2		Back pain n=3		Vomiting n=3		
	Nasopharyngitis n=2		Nasopharyngitis n=2	2	Vulvovaginal myco	otic infection n=3	
	Upper abdominal pain na	= 2	Fatigue n=2		Anxiety n=2		
	Influenza n=2		Influenza n=1		Back pain n=2		
	Pain in extremity n=1		Pain in extremity n=		Dry Mouth n=2		
	Upper resp. tract Infection	on n=2	Upper resp. tract Inf	fection n=2	Nasopharyngitis n		
	Headache n= 2		Headache n=3		Peripheral oedema		
	Procedural pain n=2		Pharyngolaryngeal p	pain n=2	Upper abdominal	pain n=1	
					Fatigue n=1		
					Influenza n=1		
					Pain in extremity r	n=1	

				. tract Infection n=1					
	oo V, Soler NG, Pahor A, Sugg J, Rohwedder doses of insulin. A randomized trial. Annals			Funding source: Astra-Zeneca and Bristol-Myers-Squibb					
				SGLT2 Inhibitor (2.5, 5 or 10 mg dapagliflozin) + insulin ± OAD versus placebo + insulin ± OAD					
	te the efficacy and safety of adding dapagliflo	, , , , , , , , , , , , , , , , , , , ,	dequately controlled with insulin with or wit	hout oral antidiabetic drugs					
Study quality	High – see quality table for further inform	ation							
Study	Multi-centre: 126 worldwide								
particulars	<b>Duration of intervention</b> : 24 weeks								
	Duration of run in: 2 week enrolment								
	Follow-up: on completion of 24 weeks, 24	week extension plus further 56 week exten	sion 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, vita	al signs							
Participant	N: 800 analysed		2						
criteria			15 kg/m²; inadequate glycaemic control (HbA						
	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)		3						
	Exclusion criteria: type 1 diabetes; signs of poorly controlled diabetes; calculated creatinine clearance <50 ml/min per 1.73 m² 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%, metforming).								
	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								
		and exercise regimen; Lead in period: uncl							
Participant	Group 1 (n analysed=193):	Group 2 (n=202):	Group 3 (n=211):	Group 4 (n=194):					
baseline data	Placebo + insulin ± OAD	2.5 mg dapagliflozin + insulin ± OAD	5 mg dapagliflozin + insulin ± OAD	10 mg dapagliflozin + insulin ± OAD					
	<b>Age:</b> 58.8 SD8.6 years	<b>Age:</b> 59.8 SD7.6 years	<b>Age:</b> 59.3 SD7.9 years	<b>Age:</b> 59.3 SD8.8 years					
	<b>Sex:</b> 49.2% male	<b>Sex:</b> 49.5% male	<b>Sex:</b> 47.4% male	<b>Sex:</b> 44.8% male					
	BMI (kg/m²): 33.1 SD5.9	<b>BMI (kg/m²):</b> 33.0 SD5.0	BMI (kg/m²): 33.0 SD5.3	BMI (kg/m²): 33.4 SD5.1					
	<b>HbA1c (%):</b> 8.47% SD0.77	<b>HbA1c (%):</b> 8.46% SD0.78	<b>HbA1c (%):</b> 8.62% SD0.89	HbA1c (%): 8.57% SD0.82					
			, ,						
	<b>Duration of diabetes:</b> 13.5 SD7.3 years <b>FPG (mmol/L):</b> 9.5 SD3.2	Duration of diabetes: 13.6 SD6.6 years FPG (mmol/L): 10.0 SD3.3	Duration of diabetes: 13.1 SD7.8 years FPG (mmol/L): 10.3 SD3.3	Duration of diabetes: 14.2 SD7.3 years FPG (mmol/L): 9.6 SD3.0					

	Systolic BP (mr	nHg): 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	ge from baseline	to study end)							
	Group 1 (n ana	lysed=193):	Group 2 (n=202):		Group 3 (n	=211):	Group 4 (n=194):  10 mg dapagliflozin + insulin ± OAD		
	Placebo + insul	in ± OAD	2.5 mg dapagliflozin + insulin ± OAD		5 mg dapa	gliflozin + insulin ± OAD			
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	
ΔHbA1c (%)	wk 24: -0.39	-0.5 to -0.28 [graph]	-0.79	-0.89 to -0.69 [graph]	-0.89	-0.99 to -0.79	-0.96	-1.06 to -0.86	
	wk 48: -0.47	-0.59 to -0.35 [graph]	-0.79	-0.9 to -0.68 [graph]	-0.96	-1.07 to -0.85	-1.01	-1.12 to -0.9	
				P<0.0001 vs placebo		p<0.0001 vs placebo		p<0.0001 vs placeb	
ΔWeight (kg)	wk 24: 0.43	0.05 to 0.81 [graph]	-0.92 -1.29 to -0.55		-1.0	-1.37 to -0.63	-1.61	-1.98 to -1.24	
	wk 48: 0.82	0.29 to 1.35 [graph]	-0.96	-1.48 to -0.44	-1.0	-1.52 to -0.48	-1.61	-2.14 to -1.08	
				p<0.0001 vs placebo		p<0.0001 vs placebo		p<0.0001 vs placeb	
ΔFPG	wk 24: NR -		-0.65	-1.19 to -0.11, p NR	-1.12	-1.66 to -0.59, p NR	-1.10	-1.64 to -0.56. p NR	
(mmol/L)	<i>wk 48:</i> NR		-0.69	-1.28 to -0.11, p NR	-0.90	-1.48 to -0.33, p NR	-0.94	-1.53 to -0.36, p NR	
				p<0.0001 vs placebo		p<0.0001 vs placebo		p<0.0001 vs placeb	
ΔSBP (mmHg)	wk 24: -3.56	-5.47 to -1.64	-4.21	-6.05 to -2.38, p NR	-5.93	-7.74 to -4.12, p NR	-6.66	-8.53 to -4.80, p NR	
	wk 48: -1.49 -3.55 to 0.57		-5.70 -7.25 to -3.34, p NR		-4.33	-6.28 to -2.38, p NR	-4.09 -6.09 to -2.09, p N		
Adverse events					-	•		<u> </u>	
Safety assessme	ent: adverse ever	nts, laboratory values, vital	signs						
-	Minor hypogh	/caemia = symptomatic epi	sode, capillary glud	cose <3.5mmol/L	General ev	rents – where frequency is	At least one of	At least one or more adverse event	
	Major hypogly	/caemia = symptomatic epi	sode, needing exte	ernal assistance with	≥5%		<b>Group 1 =</b> n=144		
	following reco	very, capillary glucose <3.0	mmol/L		UTI = Urina	ary Tract Infection	Group 2 = n=153 Group 3 = n=153 Group 4 = n=145		
	Other hypogly	caemia = suggestive criteri	a not meeting crite	eria for major or minor	GTI = Genit	tal Tract Infection			
	hypoglycaemia	a			HypoT = Hy	ypotension			
					HypoS = Hy	poglycaemia (severe)			
						lypoglycaemia (mild)	2 deaths in the 5 mg dapagliflozin grou		
					HypoO = H	ypoglycaemia (other)			
	Group 1 (n an	alysed=193):	Group 2 (n=202)	) <b>:</b>	Group 3 (n	=211):	Group 4 (n=194):		
	Placebo + insu	lin ± OAD	2.5 mg dapagliflo	ozin + insulin ± OAD	5 mg dapa	gliflozin + insulin ± OAD	10 mg dapagliflozin + insulin ± OAD		
Specific events	UTI n=10, GTI	n=5	UTI n=16, GTI n=	:13	UTI n=23, 0	GTI n=21	UTI n=20, GTI	n=21	
	HypoT n=2		HypoT n=5	iypoT n=5			HypoT n=3		
	HypoS n=2, Hy	poM n=99, HypoO n=11	HypoS n=3, HypoM n=118, HypoO n=19		HypoS n=2	, HypoM n=113, HypoO n=24	HypoS n=3, HypoM n=99, HypoO n=21		
	Renal impairm	ient / failure n=3	Renal impairment / failure n=2		Renal impairment / failure n=6		Renal impairment / failure n=4		
	Events leading	to discontinuation n=3	Events leading to	o discontinuation n=2	Events lead	ding to discontinuation n=5	Events leading to discontinuation n=5		
	Nasopharyngit	tis n=23	Nasopharyngitis	n=32	Nasophary	ngitis n=35	Nasopharyngi	tis n=25	
	Headache n=1	5	Headache n=11		Headache	n=14	Headache n=5	;	
	Back pain n=1:		Back pain n=11		Back pain r	1=8	Back pain n=1	1	
	Hypertension	n=20	Hypertension n=	:18	Hypertensi	on n=16	Hypertension	n=11	
	Diarrhoea n=8		Diarrhoea n=7		Diarrhoea	n=11	Diarrhoea n=1	.0	
	Constipation r	n=3Peripheral oedema	Constipation n=1	12	Constipation	on n=7	Constipation r	n=6	
	n=15		Peripheral oeder	ma n=8	Peripheral	oedema n=5	Peripheral oed	dema n=9	
	Upper resp. tr	act Infection n=12	Upper resp. trac	t Infection n=6	Upper resp	o. tract Infection n=8	Upper resp. tr	act Infection n=9	
	Arthralgia n=1	1	Arthralgia n=4		Arthralgia	n=3	Arthralgia n=7		



# Canagliflozin

cotransporter 2	garwal N, Polidori D, Zha inhibitor, as add-on to i					ose Fui	nding source: Janssen	Global Services				
cott ansporter 2	minibitor, as add-on to i	netioniiii iii subjects	with type 2 diabetes.	Diabetes Care 2012, 2	3(0). 1232-1236	or: ver	LT2 Inhibitor (50, 100 300 mg BD canaglifloz sus sitaglipitin + metf sus placebo + metfor	in) + metformin formin				
Aim: to assess t	ne safety, tolerability and	d efficacy of canagliflo	zin in patients with typ	e 2 diabetes who hav	e inadequate glycaem	ic control on metfor	min monotherapy					
Study quality	Medium – see quality	table for further infor	mation									
Study	Multi-centre: 85 (12 d	countries)										
particulars	Duration of intervent	tion: 12 weeks										
	Duration of run in: 4	weeks										
	Follow-up: 2 weeks p	ost-treatment										
	Design: 7-arm paralle	I group RCT, double bl	ind, placebo controlle	d								
	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 usi	ng HOMA2-%B									
	- Serum lipids											
	<ul> <li>Adverse events,</li> </ul>	laboratory assessment	ts, vital signs									
Participant	N: 451 analysed											
criteria								e (≥3 months) dose				
	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) dos of ≥1500 mg/day; stable body weight; BMI 25 (24 for Asians) to 45 kg/m²; serum creatinine <1.5mg/dl for men and <1.4mg/dl for women											
	Fuelusien eriteries no											
	Exclusion criteria: no	t specifically reported										
Interventions	Intervention 1: place											
Interventions	Intervention 1: place		D + metformin (met)			<u> </u>						
Interventions	Intervention 1: place Intervention 2: canag	bo (pla) + metformin				<b>D</b> A .						
Interventions	Intervention 1: place Intervention 2: canag Intervention 3: canag	bo (pla) + metformin diflozin (cana) 50 mg C	netformin			<b>5</b> /2/						
Interventions	Intervention 1: place Intervention 2: canag Intervention 3: canag Intervention 4: canag	bo (pla) + metformin :liflozin (cana) 50 mg C :liflozin 100 mg OD + n	netformin netformin			0/1/2						
Interventions	Intervention 1: place Intervention 2: canag Intervention 3: canag Intervention 4: canag Intervention 5: canag	bo (pla) + metformin diffozin (cana) 50 mg C diffozin 100 mg OD + n diffozin 200 mg OD + n	netformin netformin netformin			20/1						
Interventions	Intervention 1: place Intervention 2: canag Intervention 3: canag Intervention 4: canag Intervention 5: canag Intervention 6: canag	bo (pla) + metformin diffozin (cana) 50 mg C diffozin 100 mg OD + n diffozin 200 mg OD + n diffozin 300 mg OD + n	netformin netformin netformin netformin			27/1	•					
Interventions	Intervention 1: place Intervention 2: canag Intervention 3: canag Intervention 4: canag Intervention 5: canag Intervention 6: canag Intervention 7: sitagli	bo (pla) + metformin cliflozin (cana) 50 mg C cliflozin 100 mg OD + n cliflozin 200 mg OD + n cliflozin 300 mg OD + n cliflozin 300 mg BD + m	netformin netformin netformin netformin + metformin			20/1	•					
nterventions	Intervention 1: place Intervention 2: canag Intervention 3: canag Intervention 4: canag Intervention 5: canag Intervention 6: canag Intervention 7: sitagli OAD schedule: metfo	bo (pla) + metformin cliflozin (cana) 50 mg C cliflozin 100 mg OD + n cliflozin 200 mg OD + n cliflozin 300 mg OD + n cliflozin 300 mg BD + m cliflozin 300 mg BD + m cptin (sita) 100 mg OD	netformin netformin netformin netformin + metformin SD479 mg/day			20/1						
	Intervention 1: place Intervention 2: canag Intervention 3: canag Intervention 4: canag Intervention 5: canag Intervention 6: canag Intervention 7: sitagli OAD schedule: metfo	bo (pla) + metformin difflozin (cana) 50 mg C difflozin 100 mg OD + n difflozin 200 mg OD + n difflozin 300 mg OD + n difflozin 300 mg BD + m difflozin 300 mg OD dirmin mean dose 1890	netformin netformin netformin netformin + metformin SD479 mg/day	<b>Group 3</b> cana	Group 4 cana	Group 5 cana	<b>Group 6</b> cana	<b>Group 7</b> sita				
Participant	Intervention 1: place Intervention 2: canag Intervention 3: canag Intervention 4: canag Intervention 5: canag Intervention 6: canag Intervention 7: sitagli OAD schedule: metfo	bo (pla) + metformin diffozin (cana) 50 mg C diffozin 100 mg OD + n diffozin 200 mg OD + n diffozin 300 mg OD + n diffozin 300 mg BD + m diptin (sita) 100 mg OD dirmin mean dose 1890 eatment screening ph	netformin netformin netformin + metformin SD479 mg/day ase Group 2 cana	Group 3 cana 100 mg OD + met				•				
Participant	Intervention 1: place Intervention 2: canag Intervention 3: canag Intervention 4: canag Intervention 5: canag Intervention 6: canag Intervention 7: sitagli OAD schedule: metfo	bo (pla) + metformin diffozin (cana) 50 mg C diffozin 100 mg OD + n diffozin 200 mg OD + n diffozin 300 mg OD + n diffozin 300 mg BD + m diffozin 300 mg OD diffozin 300 mg OD diffozin 300 mg OD diffozin mean dose 1890 eatment screening ph	netformin netformin netformin netformin + metformin SD479 mg/day ase	•	<b>Group 4</b> cana	Group 5 cana	Group 6 cana	•				
Interventions Participant baseline data	Intervention 1: place Intervention 2: canag Intervention 3: canag Intervention 4: canag Intervention 5: canag Intervention 6: canag Intervention 7: sitagli OAD schedule: metfo	bo (pla) + metformin diffozin (cana) 50 mg C diffozin 100 mg OD + n diffozin 200 mg OD + n diffozin 300 mg OD + n diffozin 300 mg BD + m diffozin 300 mg OD diffozin 300 mg OD diffozin 300 mg OD diffozin mean dose 1890 eatment screening ph	netformin netformin netformin hetformin + metformin SD479 mg/day ase  Group 2 cana 50 mg OD + met	100 mg OD + met	Group 4 cana 200 mg OD + met	Group 5 cana 300 mg OD + met	Group 6 cana 300 mg BD + met	100 mg OD + me				

	BMI (kg/m <sup>2</sup> )	30.6 SD4.6	31.7	SD4.6	31.7 SD	5.0	31.4 SD5.2		31.6 S	D4.9	31.8 SD5.2	31.6 SD5.0	
	HbA1c (%)	7.75 SD0.83			99 7.83 SD0.9				7.69 S		7.73 SD0.89	7.64 SD0.95	
	Diab. duration (yea			D5.0	6.1 SD4		6.4 SD5.7		5.9 SD5.2		5.8 SD4.6	5.6 SD4.7	
	FPG (mmol/L)	9.1 SD2.1		D2.5	9.3 SD2		8.9 SD2.1		8.8 SD		8.7 SD1.9	8.8 SD2.3	
	SBP (mmHg)	125 SD10		SD11	127 SD1		124 SD11		126 SD12		128 SD13	129 SD13	
Outcome (change	ge from baseline at st		12/	JD11	127301	.5	12+3011	I	120 31	712	120 30 13	125 30 15	
Outcome (chang	Group 1 pla + met	Group 2 cana 5	n mg OD	Group 3	cana	Group 4	rana	Group	Cana	G	roup 6 cana	Group 7 sita 100 mg	
	(n=65)	•	-		100 mg OD + met		•		•		00 mg BD + met	OD + met (n=65)	
	(11-03)	1 11101 (11-04)					OD THICK	(n=64)			=64)	OD 1 met (n=05)	
Δ <b>HbA1c (%)</b> [SE	-0.22 SE0.08	-0.79 SE0.1	•		Π 12	-0.70 SE	U U8	-0.92 SE	:n ng	•	.95 SE0.08	-0.74 SE0.08	
from graph]	0.22 320.00	p<0.001 vs plac	oho		vs placebo		vs placebo	p<0.001		_	<0.001 vs placebo	p<0.001 vs placebo	
ΔWeight (kg)	-1.1 SE0.29	-2.3 SE0.39	EDU	-2.6 SE0	•	-2.7 SE0		-3.4 SEC			.4 SE0.29	-0.6 SE0.39	
[SE from graph]	-1.1 360.29	p<0.001 vs plac	oho		vs placebo		vs placebo	p<0.001			.4 3E0.29 <0.001 vs placebo	NS vs placebo	
ΔFPG (mmol/L)	10.2 SE0.20	-0.9 SE0.22	EDU	-1.4 SE0		-1.5 SEO		-1.4 SEC	•		.3 SE0.20	-0.7 SE0.20	
	+0.2 SE0.20		oho									-0.7 SEU.20 p NR	
[SE from graph]	4.2.654.5	p<0.001 vs plac			vs placebo		vs placebo	p<0.001			0.001 vs placebo	•	
ΔSBP (mmHg)	-1.3 SE1.5	-0.9 SE1.7, p NR		+1.0 SE1	3, p NK	-2.1 SE1	.8, p NR	-4.9 SE1	1.5, p NR -3.6 SE1.4, p NR		.6 SE1.4, p NR	-0.8 SE1.4, p NR	
Adverse events		. /24 !! 15! !!									16 1 1 1 1 1		
Safety assessme	·	orts (Medical Dictiona			•	<u> </u>							
		ia (HypoM) = sympton	natic episc		UTI = Urinary Tract Infection  GTI = Genital Tract Infection  Hypo = Hypoglycaemia					At least one or more adverse event  Group 1 = n=26  Group 2 = n=32  Group 3 = n=30			
	capillary glucose <3.5												
		nia (HypoS) = sympton											
	-	istance with following	recovery,										
	capillary glucose <3.0			Нур	HypoT = AEs suggestive of		f hypotension			<b>Group 4 =</b> n=26			
		<b>a</b> (HypoO) = symptom	is, but						<b>Group 5 =</b> n=2				
	without measureme	nt confirming								•	<b>roup 6 =</b> n=36		
										<b>Group 7 =</b> n			
		<b>Group 1</b> pla (n=65)	Group 2		Group 3 ca		Group 4 cana		roup 5		Group 6 cana	Group 7 sita	
			50 mg O	D (n=64)	100 mg OD	(n=64)	200 mg OD (n	1=65) 3	00 mg	OD (n=64)	300 mg BD (n=64)	100 mg OD (n=65	
Specific	UTI	n=4	n=3		n=2		n=6		=2		n=3	n=1	
Events	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	i=0		n=2	n=3	
	НуороТ	n=1	n=0		n=4		n=3		=1		n=1	n=1	
	AEs leading to	n=2	n=1		n=3		n=1	n	=2		n=2	n=0	
	discontinuation												
	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	n=0	n=4		n=2		n=4	n	=1		n=3	n=1	
	mycotic infect.												

**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% Cl -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% Cl -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. 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, <sup>2;3</sup> 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).<sup>4</sup>

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.<sup>5</sup>

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.<sup>6</sup>

# **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.<sup>7</sup>

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
  - o 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<sup>6</sup> 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. 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<sup>2</sup> 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.

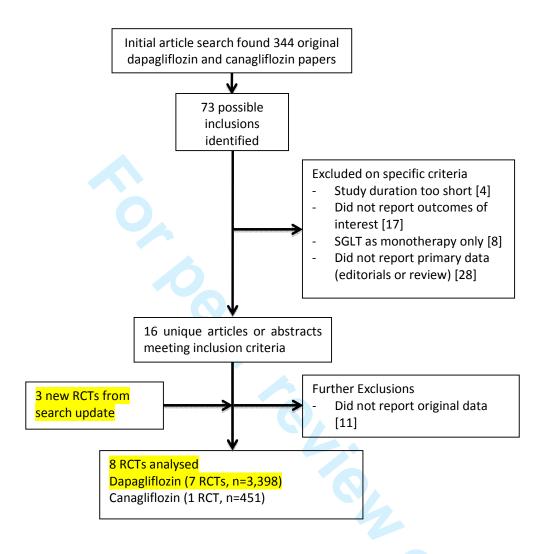
No meta-analysis using active comparators was performed due to clinical heterogeneity. Only two trials had active comparators, glipizide and sitagliptin, which have different modes of action and different effects on weight and hypoglycaemia risk.

## **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.<sup>8-15</sup> The dapagliflozin trials included 3,398 participants. In the single canagliflozin trial, <sup>16</sup> 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)<sup>9</sup> 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,<sup>8;9;11;16</sup> insulin,<sup>15</sup> glimepiride,<sup>13</sup> thiazolidinedione (TZD),<sup>12</sup> or combination therapy.<sup>14;15</sup>

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

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, 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 <sup>8</sup>	<b>N:</b> 534	Intervention: 2.5, 5 or 10 mg	<b>HbA1c (%):</b> -0.54 (-0.74, -0.34)
Design: multi-centre (n=80), 4-arm,	Age (years): 54 to 55 SD9 to 10	dapagliflozin once daily	Weight (kg): -2.00 (-2.67, -1.33)
double blind, placebo controlled RCT	<b>HbA1c (%):</b> 7.9 to 8.2 SD0.8 to 1.00	Comparator: placebo	FPG (mmol/L): -0.97 (95% CI NR)
Duration: 24 weeks	<b>BMI (kg/m²):</b> 31.2 to 31.8 SD5.4 to 6.2	Background antidiabetic therapy:	SBP (mmHg): -4.9 (95% CI NR)
Follow-up: 102 weeks		metformin (≥1500 mg/day)	
Quality: high			
Bolinder 2012 <sup>9;10</sup>	N: 180	Intervention: 10 mg dapagliflozin once	HbA1c (%): -0.29 (-0.42, -0.16)
Design: multi-centre (n=40), 2-arm,	Age (years): 61 SD7 to 8	<mark>daily</mark>	Weight (kg): -2.08 (-2.84, -1.32)
double blind, placebo controlled RCT	<b>HbA1c (%):</b> 7.2 SD0.4 to 0.5	Comparator: placebo	<b>FPG (mmol/L):</b> -0.95 (-1.33, -0.57)
Duration: 24 weeks	BMI (kg/m <sup>2</sup> ): 31.7 to 32.1 SD3.9	Background antidiabetic therapy:	SBP (mmHg): -2.8 (-5.9, 0.2)
Follow-up: 78 week extension		metformin (≥1500 mg/day)	
<mark>Quality:</mark> high			
Nauck 2011 <sup>11</sup>	N: 801	Intervention: dapagliflozin once daily	<b>HbA1c (%):</b> 0.0 (-0.11, +0.11)
Design: multi-centre (n=95), 2-arm,	Age (years): 58 to 59 SD9 to 10	(mean dose 9.2 mg)	Weight (kg): -4.66 (-5.15, -4.17)
double blind, active controlled RCT	<b>HbA1c (%):</b> 7.7 SD0.9	Comparator: glipizide (mean dose	FPG (mmol/L): -0.20 (95% CI NR)
Duration: 52 weeks	<b>BMI (kg/m<sup>2</sup>):</b> 31.2 to 31.7 SD5.1	16.4 mg)	SBP (mmHg): -5.1 (95% CI NR)
Follow-up: 156 week extension		Background antidiabetic therapy:	
Quality: high		metformin (≥1500 mg/day)	
Rosenstock 2012 <sup>12</sup>	N: 420	Intervention: 5 or 10 mg dapagliflozin	HbA1c (%): -0.55 (-0.71, -0.39)
Design: multi-centre (n=105), 3-arm,	Age (years): 53 to 54 SD10 to 11	once daily	Weight (kg): -1.78 (-2.32, -1.24)
double blind, placebo controlled RCT	<b>HbA1c (%):</b> 8.3 to 8.4 SD1.0	Comparator: placebo	FPG (mmol/L): -1.33 (95% CI NR)
<mark>Duration: 24 weeks</mark>	<b>BMI</b> (kg/m <sup>2</sup> ): 51 to 62% $\geq$ 30; 87 to 93%	Background antidiabetic therapy:	SBP (mmHg): -4.7 (95% CI NR)
F <mark>ollow-up:</mark> 24 week extension	<mark>≥25</mark>	pioglitazone (30 or 45 mg/day)	
<mark>Quality:</mark> low			
Strojek 2011 <sup>13</sup>	N: 592	Intervention: 2.5, 5 or 10 mg	<b>HbA1c (%):</b> -0.69 (-0.87, -0.51)
Design: multi-centre (n=84), 4-arm,	Age (years): 59 to 60 SD8 to 10	dapagliflozin once daily	Weight (kg): -1.54 (-1.88, -1.20)
double blind, placebo controlled RCT	<b>HbA1c (%):</b> 8.1 SD0.7 to 0.8	Comparator: placebo	FPG (mmol/L): -1.47 (-1.86, -1.08)
Ouration: 24 weeks	<b>BMI</b> (kg/m <sup>2</sup> ): 45 to 51% $\geq$ 30; 80 to 86%	Background antidiabetic therapy:	SBP (mmHg): -3.8 (-6.4, -1.2)
Follow-up: 24 week extension	≥25	glimepiride (4 mg)	
Quality: high			

Study design	Participants	Interventions	Outcomes
Wilding 2009 <sup>14</sup>	N: 71	Intervention: 10 or 20 mg dapagliflozin	HbA1c (%): -0.70 (-1.07, -0.33)
Design: multi-centre (n=26), 3-arm,	Age (years): 56 to 58 SD7 to 11	once daily	Weight (kg): -2.60 (-3.94, -1.26)
double blind, placebo controlled RCT	<b>HbA1c (%):</b> 8.4 to 8.5 SD0.7 to 0.9	Comparator: placebo	FPG (mmol/L): -0.86 (-2.13, +0.42)
Ouration: 12 weeks	<b>BMI (kg/m²):</b> 34.8 to 36.2 SD3.6 to 4.6	Background antidiabetic therapy:	SBP (mmHg): NR
Follow-up: 4 weeks		insulin (51 to 56 U) + OAD (≤79%	
Quality: medium		metformin only, ≤25% metformin plus	
		TZD, ≤12.5% TZD only)	
Wilding 2012 <sup>15</sup>	N: 800	Intervention: 2.5, 5 or 10 mg	HbA1c (%): -0.57 (-0.67, -0.40)
Design: multi-centre (n=126), 4-arm,	Age (years): 59 to 60 SD8 to 9	dapagliflozin once daily	Weight (kg): -2.04 (-2.57, -1.51)
double blind, placebo controlled RCT	HbA1c (%): 8.5 to 8.6 SD0.8 to 0.9	Comparator: placebo	FPG (mmol/L): NR
<mark>Duration: 24 weeks</mark>	BMI (kg/m <sup>2</sup> ): 33.0 to 33.4 SD5.0 to 5.9	Background antidiabetic therapy:	SBP (mmHg): -3.11 (-5.79, -0.43)
Follow-up: 24 + 56 week extension		insulin (77.1 U) ± OAD (~50% none,	
<mark>Quality:</mark> high		~40% metformin only, rest combination)	
Canagliflozin			Difference versus active / placebo (95%
			CI)
Rosenstock 2012 <sup>16</sup>	N: 451	<b>Intervention:</b> 50, 100, 200 or 300 mg OD	
Design: multi-centre (n=85), 7-arm,	Age (years): 52.9 SD8.1	or 300 mg BD canagliflozin	+0.04 to -0.21 vs sitagliptin (95% CI NR)
double blind, placebo and active	HbA1c (%): 7.75 SD0.93	Comparator 1: placebo	Weight (kg): -1.2 to -2.3 vs placebo;
controlled RCT	<b>BMI (kg/m²):</b> 31.5 SD4.9	Comparator 2: 100 mg OD sitagliptin	-1.7 to -2.8 vs sitagliptin (95% CI NR)
Ouration: 12 weeks		Background antidiabetic therapy:	<b>FPG (mmol/L):</b> -1.1 to -1.7 vs placebo;
Follow-up: 2 weeks		metformin (≥1500 mg)	-0.2 to -0.8 vs sitagliptin (95% CI NR)
Qualitus madium			SBP (mmHg): +2.3 to -3.6 vs placebo;
Quality: medium			
quanty: medium			+1.8 to -4.1 vs sitagliptin (95% CI NR)
quanty: medium			+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 <sup>8</sup>	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 <sup>9;10</sup>	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 <sup>11</sup>	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 <sup>12</sup>	Not reported	Not reported	Yes (double blind)	Not reported	8% at 24 weeks, 19% at 48 weeks	Yes	<b>Unclear</b>	Not reported	Astra-Zeneca and Bristol- Myers-Squibb
Strojek 2011 <sup>13</sup>	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 <sup>14</sup>	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 <sup>15</sup>	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 <sup>16</sup>	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)<sup>16</sup> 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)<sup>9</sup>. 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).

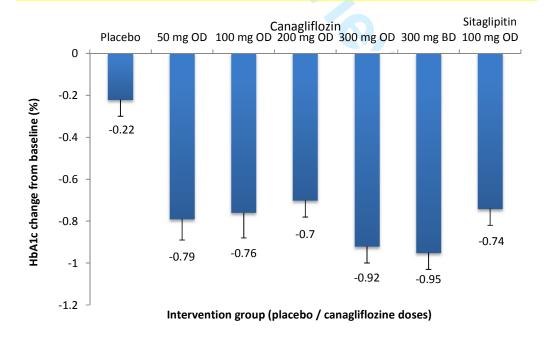
In the study by Nauck 2011,<sup>11</sup> there was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by -0.52% (95% CI: -0.60, -0.44).

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

	Dapaglif	lozin (10 r	mg)	Pla	cebo			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
1.1.1 up to 26 weeks									
Bailey 2010	-0.84	0.82	132	-0.3	0.83	134	10.1%	-0.54 [-0.74, -0.34]	
Bolinder 2012	-0.39	0.46	83	-0.1	0.42	86	13.3%	-0.29 [-0.42, -0.16]	
Rosenstock 2012	-0.97	0.67	140	-0.42	0.67	139	12.0%	-0.55 [-0.71, -0.39]	-
Strojek 2011	-0.82	0.75	150	-0.13	0.79	143	11.1%	-0.69 [-0.87, -0.51]	
Wilding 2009	-0.61	0.58	23	0.09	0.62	19	4.9%	-0.70 [-1.07, -0.33]	<del></del>
Wilding 2012 Subtotal (95% CI)	-0.96	0.67	173 <b>701</b>	-0.39	0.72	166 <b>687</b>	12.5% <b>63.9%</b>	-0.57 [-0.72, -0.42] -0.54 [-0.67, -0.40]	•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	,	,	5 (P = 0	).006); I <sup>2</sup> = 7	0%				
rest for overall effect.	Z = 7.50 (i	0.00001)							
1.1.2 48 weeks and m	ore								
Bolinder 2012	-0.38	0.51	79	0.02	0.51	77	11.9%	-0.40 [-0.56, -0.24]	
Rosenstock 2012	-1.21	0.58	140	-0.54	0.67	139	12.5%	-0.67 [-0.82, -0.52]	
Wilding 2012 Subtotal (95% CI)	-1.01	0.72	164 383	-0.47	0.77	157 <b>373</b>	11.7% <b>36.1</b> %	-0.54 [-0.70, -0.38] -0.54 [-0.69, -0.38]	•
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup> = \$	5.93, df = 2	2 (P = 0.	05); I <sup>2</sup> = 66%	6				
Test for overall effect:	Z = 6.78 (P <	0.00001)							
Total (95% CI)			1084			1060	100.0%	-0.54 [-0.63, -0.44]	•
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup> = 2	22.81, df =	8 (P = 0	0.004); I <sup>2</sup> = 6	5%			_	-1 -0.5 0 0.5 1
Took for account offerst.	Z = 10.99 (P	< 0.00001	)					Favr	ا د.ت د. د. د. ا Durs dapagliflozin Favours placeb
Test for overall effect:				$0.55$ ), $I^2 = 0$				Tavo	rais aapagiiiloziii - i avouls platet

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). 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

	Dapagli	flozin (10	mg)	PI	acebo	)		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	IV, Random, 95% CI
1.2.1 up to 26 weeks									
Bailey 2010	-2.9	2.62	133	-0.9	2.95	136	10.5%	-2.00 [-2.67, -1.33]	<del></del>
Bolinder 2012	-2.96	2.61	89	-0.88	2.62	91	8.3%	-2.08 [-2.84, -1.32]	<del></del>
Rosenstock 2012	-0.14	2.3	140	1.64	2.3	139	14.8%	-1.78 [-2.32, -1.24]	<del></del>
Strojek 2011	-2.26	1.5	151	-0.72	1.47	145	27.8%	-1.54 [-1.88, -1.20]	-
Wilding 2009	-4.5	2.31	23	-1.9	2.26	22	3.0%	-2.60 [-3.94, -1.26]	<del></del>
Wilding 2012	-1.61	2.51	177	0.43	2.51	168	15.2%	-2.04 [-2.57, -1.51]	<del></del>
Subtotal (95% CI)			713			701	79.5%	-1.81 [-2.04, -1.57]	<b>♦</b>
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi² =	= 5.30, df	= 5 (P =	0.38); I	$^{2} = 6\%$				
Test for overall effect:	Z = 15.17 (F	P < 0.000	01)						
1.2.2 48 weeks and m	ore								
Bolinder 2012	-4.39	4.14	81	-2.03	4.03	84	3.4%	-2.36 [-3.61, -1.11]	<del></del>
Rosenstock 2012	0.69	3	140	2.99	3.4	139	8.5%	-2.30 [-3.05, -1.55]	<del></del>
Wilding 2012	-1.61	3.48	166	0.82	3.39	157	8.6%	-2.43 [-3.18, -1.68]	<del></del>
Subtotal (95% CI)			387			380	20.5%	-2.36 [-2.85, -1.88]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> =	= 0.06, df	= 2 (P =	0.97); [	<sup>2</sup> = 0%				
Test for overall effect:			,						
Total (95% CI)			1100			1081	100.0%	-1.95 [-2.18, -1.71]	<b>•</b>
Heterogeneity: Tau <sup>2</sup> =	0.02; Chi <sup>2</sup> =	= 9.69, df	= 8 (P =	0.29); [	<sup>2</sup> = 17 <sup>9</sup>	%			+ + + + + + + + + + + + + + + + + + + +
Test for overall effect:			,	,,				,	-4 -2 0 2
Test for subgroup diffe	,		,	= 0.04	)  2 = 7	76.9%		1	Favours experimental Favours control

## 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).<sup>16</sup>

## 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.<sup>11</sup>

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). <sup>16</sup>

# **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.<sup>16</sup>

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. <sup>14</sup> 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. <sup>13</sup> 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). <sup>11</sup>

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.<sup>16</sup>

# Other adverse events

Three studies reported deaths in dapagliflozin groups (Bolinder 2011 (one death), Strojek 2011 (two deaths), Wilding 2012 (two deaths)). Strojek 2011 (two deaths), Strojek 2011 (two deaths), Wilding 2012 (two deaths)). Strojek 2011 (two deaths), Wilding 2012 (two deaths)). Strojek 2011 (two deaths), Strojek 2011 (

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). 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.

#### **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. <sup>17</sup> 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<sup>18</sup>), 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<sup>19</sup>) 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%. <sup>21</sup>

Musso et al. (2012)<sup>21</sup> 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. 47<sup>th</sup> 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. 72<sup>nd</sup> 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

	JL, Pieters A, Bastien A, List JF. <b>Effect of dap</b> andomised, double-blind, placebo-controlle		who have inadequate glycaemic control with	Funding source: Astra-Zeneca and Bristol-Myers-Squibb				
				SGLT2 inhibitor (2.5, 5 or 10 mg dapagliflozin) + metformin versus placebo + metformin				
Aim: to determ	ine 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	ation						
Study	Multi-centre: 80 (USA, Canada, Argentina,	Mexico, Brazil)						
particulars	<b>Duration of intervention</b> : 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 I	olind, placebo controlled						
	Primary outcome: change from baseline in	HbA1c at week 24						
	Secondary outcomes:							
	At 24 weeks changes in:							
	<ul> <li>Fasting plasma glucose</li> </ul>							
		Lc <7%, number with HbA1c of 9% or more						
		ne in bodyweight, and decreases in bodywe	eight of 5% or more					
	<ul> <li>Laboratory tests, adverse events</li> </ul>							
Participant	N: 534 analysed		3					
criteria		en 18 and 77 years; type 2 diabetes; BMI ≤4	5 kg/m <sup>2</sup> ; HbA1c 7 to 10.0%; fasting C-peptide	e ≥0.34 ng/ml; taking stable dose				
	metformin ≥1500 mg per day	16.6						
			consistent with metformin labelling); urine a					
		•	oper limit of normal, symptoms of poorly con	· · · · · · · · · · · · · · · · · · ·				
	1	loss during the 3 months before enrolment)	; systolic blood pressure ≥180 mmHg or diast	olic blood pressure 2110 mmHg; any				
Interventions	significant other systemic disease  Intervention 1: 2.5 mg dapagliflozin + met	formin						
interventions	Intervention 1: 2.5 mg dapagliflozin + metfo							
	Intervention 2: 5 mg dapagliflozin + metfo							
	Intervention 4: matching placebo + metfor							
			mg/day); dapagliflozin once daily before mo	rning meal				
	All groups: diet and exercise counselling	se (£1300 mg/day, mean dose 1732 to 1801	mig/day), dapagimozini once dany before mo	Tillig frical				
		ssess compliance with placeho inatients ran	domised after successful completion; metfor	min dose (onen lahel 500 mg tahlets)				
	continued at pre-study levels	ssess compliance with placebo, patients rail	domised after successful completion, metror	min dose (open label 500 mg tablets)				
Participant	Group 1 (n analysed=134):	Group 2 (n=135):	Group 3 (n=133):	Group 4 (n=132):				
baseline data	Placebo OD + metformin	2.5 mg dapagliflozin OD + metformin	5 mg dapagliflozin OD + metformin	10 mg dapagliflozin OD + metformin				
	<b>Age:</b> 53.7 SD10.3 years	Age: 55.0 SD9.3 years	<b>Age:</b> 54.3 SD9.4 years	Age: 52.7 SD9.9 years				
	1.01.0002.20.0 / 00.0	<b>Sex:</b> 51% male	<b>Sex:</b> 50% male	<b>Sex:</b> 57% male				

	BMI (kg/m²): 31 HbA1c (%): 8.11			BMI (kg/m²): 31.6 SD4.8 HbA1c (%): 7.99% SD0.90		BMI (kg/m <sup>2</sup> ): 31.4 SD5.0 HbA1c (%): 8.17% SD0.96		BMI (kg/m²): 31.2 SD5.1 HbA1c (%): 7.92% SD0.82	
	Duration of dial	petes: 5.8 SD5.1 years	Duration of	of diabetes: 6.0 SD6.2 years	Duration of diabetes: 6.4 SD5.8 years		Duration of o	<b>Duration of diabetes:</b> 6.1 SD5.4 years	
	FPG (mmol/L): 9.19 SD2.57 Systolic BP (mmHg): 127.7 SD14.6			I/L): 8.96 SD2.39	FPG (mmol/L): 9.39 SD2.72			.): 8.66 SD2.15	
			-	(mmHg): 126.6 SD14.5	-	P (mmHg): 126.9 SD14.3	•	mmHg): 126.0 SD15.9	
Outcome (chan		to study end (week 24))	•	· · · · · · · · · · · · · · · · · · ·				- Or	
•	Group 1 (n=134	• • • • • • • • • • • • • • • • • • • •	Group 2 (n	Group 2 (n=135):		Group 3 (n=133):		.32):	
	Placebo OD + m	etformin	2.5 mg dag	pagliflozin OD + metformin	5 mg dap	agliflozin OD + metformin	10 mg dapag	liflozin 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	-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	
(mmol/L)				p=0.0019 vs placebo		p<0.0001 vs placebo		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	
Safety assessm						.1) via patient questionnaire an			
Surety assessin		caemia = symptomatic epis				events – where frequency is		or more adverse event	
		caemia = symptomatic epis			>5%		<b>Group 1 =</b> n=88		
		ery, capillary glucose <3.0n	_		UTI = Urir	nary Tract Infection	Group 2 = n=	89	
		,, , , , ,	•			ital Tract Infection	Group 3 = n=	95	
					HypoT = H	Hypotension	Group 4 = n=		
					HypoG = I	Hypoglycaemia	·		
	Group 1 (n ana	lysed=134):	Group 2 (n	= 135):	Group 3 (		Group 4 (n=	132):	
	Placebo OD + r	netformin	2.5 mg dar	pagliflozin OD + metformin	5 mg dap	agliflozin OD + metformin	10 mg dapag	liflozin OD + metformin	
Specific events	UTI n=11, GTI n	=7	UTI n= 6, G	GTI n=11	UTI n=10,	GTI n=18	UTI n=16, GT	l n=12	
	HypoT n=1, Hyp	ooG n=4	HypoT n=0	, HypoG n=3	HypoT n=	2, HypoG n=5	HypoT n=0, H	lypoG n=5	
	Events leading	to discontinuation n=5	Events lead	ding to discontinuation n=3	Events lea	ading to discontinuation n=3	Events leadin	g to discontinuation n=4	
	Diarrhoea n=7		Diarrhoea	n=3	Diarrhoea	n=5	Diarrhoea n=	10	
	Back pain n=7		Back pain i	n=5	Back pain	n=3	Back pain n=:	10	
	Nasopharyngiti	s n=11	Nasophary	ngitis n=12	Nasophar	ryngitis n=4	Nasopharyng	ritis n=8	
	Cough n=7		Cough n=4		Cough n=	4	Cough n=1		
	Influenza n=10		Influenza r	1=13	Influenza	n=13	Influenza n=8	3	
	Hypertension n	=6	Hypertens	ion n=9	Hyperten	sion n=4	Hypertension	n n=5	
		ct Infection n=10		o. tract Infection n=5	Upper res	sp. tract Infection n=4		ract Infection n=3	
	Headache n=6		Headache	n=4	Headache n=1		Headache n=11		

	n Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, Sugg J, Parikh S. <mark>Effects of dapagliflozin on body weight, total fat mass,</mark> se tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. Journal of	Funding source: Astra-Zeneca and Bristol-Myers-Squibb							
	gy and Metabolism 2012; 97(3): 1020-1031 <sup>9</sup>	Bristoi-Wyers-Squibb							
		SGLT2 inhibitor (10 mg dapagliflozin) + metformin							
	er J, Johansson L, Langkilde AM, Sjöström CD, Sugg J, Parikh S. Dapagliflozin has no effect on markers of bone formation and	versus placebo + metformin							
	mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes, Obesity and E-publication ahead of print] <sup>10</sup>	Total places in the second							
	e-publication alread of print; ight to be provided the control of	nadaguata glusasa santral with							
metformin	ight loss with dapagimozh, and establish effect on body composition and bone metabolish in patients with type 2 diabetes with i	nadequate glucose control with							
Study quality	High – see quality table for further information								
Study particulars	Multi-centre: 40 (Bulgaria, Czech Republic, Hungary, Poland, Sweden)								
Study particulars	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								
<mark>Participant</mark>	N: 180 analysed								
<mark>criteria</mark>	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 <sup>2</sup> ; 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								
	stimulating hormone level; 25-hydroxyvitamin D level <12 ng/mL (<30 nmol/L); history of osteoporotic fracture, and other skele								
	similar within 6 months of enrolment; SBP ≥180 mmHg and/or DBP ≥110 mmHg; congenital renal glycosuria; significant cardiac								
	haematological, oncological, endocrine, immunological (including hypersensitivity to study medications), and alcohol and/or su	bstance misuse disorders; pregnancy							
	and/or lactation; a history of bariatric surgery; use of weight loss medication within 30 days of enrolment								
<b>Interventions</b>	Intervention 1: 10 mg dapagliflozin + metformin								
	Intervention 2: placebo + metformin  2.20 ask duly metformin at the study days (21500 mg/day mean days 1001 mg SD430 in Group 1, 1000 mg SD477 in Group 1	N. danagliflarin anga daile bafaga ay with							
	OAD schedule: metformin at pre-study dose (≥1500 mg/day, mean dose 1901 mg SD430 in Group 1, 1989 mg SD477 in Group 2	g); dapagiiflozin 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	Group 1 (start n= 91, analysed r	(start n= 91, analysed n=91): Placebo + metformin Group 2 (start n= 91, analysed n= 89): 10 mg dapagliflo						
<mark>baseline data</mark>	<b>Age:</b> 60.8 SD6.9 years		Age: 60.6 SD8.2 years					
	Sex: 56% male		<b>Sex:</b> 55.1% male	,				
	BMI (kg/m <sup>2</sup> ): 31.7 SD3.9		BMI (kg/m <sup>2</sup> ): 32.1 SD	9 <mark>3.9</mark>				
	HbA1c (%): 7.16% SD0.53		HbA1c (%): 7.19% SD	<mark>0.44</mark>				
	<b>Duration of diabetes: 5.5 SD5.3</b>	years years	<b>Duration of diabetes</b>	:: 6.0 SD4.5 years				
	FPG (mmol/L): 8.3 SD1.4		FPG (mmol/L): 8.2 SD	<mark>01.4</mark>				
Outcome (change)	from baseline to study end (24 wee	<mark>eks))</mark>						
	Group 1 (n=91): Placebo + metfo	<mark>ormin</mark>	Group 2 (n= 89): 10 n	ng dapagliflozin + metformin				
	Mean	<mark>95% CI</mark>	<mark>Mean</mark>	<mark>95% CI</mark>				
ΔHbA1c (%)	-0.10	-0.01 to -0.19 [from graph]	<mark>-0.39</mark>	-0.29 to -0.49 [from graph] , p<0.0001 vs placebo				
ΔWeight (kg)	-0.88	-1.43 to -0.34	<mark>-2.96</mark>	-3.51 to -2.41, p<0.0001 vs placebo				
ΔFPG (mmol/L)	+0.13	NR A	<mark>-0.82</mark>	NR, p<0.0001 vs placebo				
	Mean	SD	Mean	SD				
ΔSBP (mmHg)	0.1	NR	<mark>-2.7</mark>	NR NR				
Adverse events			<u> </u>					
Safety assessment	t: assessed via adverse events from	the Medical Dictionary or Regulatory Activities	(MedDRA v12.1) via patie	ent questionnaire and active questioning during visits, labor				
tests and vital signs			, ,					
		= symptomatic episode, capillary glucose	General events – who	ere At least one or more adverse event				
			frequency is >2%  Group 1 = 42.9%					
<3.5mmol/L, asymptomatic episode with glucose <3.5 mmol/L Severe hypoglycaemia (HypoS) = symptomatic episode needing external			UTI = Urinary Tract Infection Group 2 = 39.6%					
			UTI = Utiliary Tract in	fection   <b>Group 2 = 39.6%</b>				
			GTI = Genital Tract In					
	assistance with capillary glucose	= symptomatic episode needing external e <3.0mmol/L, recovery following glucose or	GTI = Genital Tract In	<mark>fection</mark>				
	assistance with capillary glucose glucagon administration	e <3.0mmol/L, recovery following glucose or	GTI = Genital Tract In HypoS = Hypoglycaen	fection nia (severe)  1 death in dapagliflozin group, no deaths i				
	assistance with capillary glucose glucagon administration Other hypoglycaemia (HypoO) =		GTI = Genital Tract In HypoS = Hypoglycaen HypoM = Hypoglycae	fection  inia (severe)  1 death in dapagliflozin group, no deaths i placebo group				
	assistance with capillary glucose glucagon administration	e <3.0mmol/L, recovery following glucose or	GTI = Genital Tract In HypoS = Hypoglycaen HypoM = Hypoglycae HypoO = Hypoglycaen	riction  mia (severe)  1 death in dapagliflozin group, no deaths i placebo group  mia other				
	assistance with capillary glucose glucagon administration Other hypoglycaemia (HypoO) =	e <3.0mmol/L, recovery following glucose or	GTI = Genital Tract In HypoS = Hypoglycaen HypoM = Hypoglycae	riction  mia (severe)  1 death in dapagliflozin group, no deaths i placebo group  mia other				
	assistance with capillary glucose glucagon administration Other hypoglycaemia (HypoO) =	<3.0mmol/L, recovery following glucose or symptoms, but without confirmative	GTI = Genital Tract In HypoS = Hypoglycaen HypoM = Hypoglycae HypoO = Hypoglycae HypoT = Hypotension	fection nia (severe) 1 death in dapagliflozin group, no deaths i placebo group mia other No significant effect on bone formation an resorption or bone mineral density				
Specific events	assistance with capillary glucose glucagon administration Other hypoglycaemia (HypoO) = measurement  Group 1 (n=91): Placebo + metfo	<3.0mmol/L, recovery following glucose or symptoms, but without confirmative	GTI = Genital Tract In: HypoS = Hypoglycaen HypoM = Hypoglycae HypoO = Hypoglycaen HypoT = Hypotension  Group 2 (n= 89): 10 n	fection  mia (severe)  1 death in dapagliflozin group, no deaths i placebo group  mia other  No significant effect on bone formation an				
Specific events	assistance with capillary glucose glucagon administration Other hypoglycaemia (HypoO) = measurement  Group 1 (n=91): Placebo + metfo	e <3.0mmol/L, recovery following glucose or esymptoms, but without confirmative or entire or esymptoms.	GTI = Genital Tract In: HypoS = Hypoglycaen HypoM = Hypoglycaen HypoO = Hypoglycaen HypoT = Hypotension  Group 2 (n= 89): 10 n  UTI n=6, GTI n=3	fection mia (severe) 1 death in dapagliflozin group, no deaths i mia (mild) mia other No significant effect on bone formation an resorption or bone mineral density mg dapagliflozin + metformin				
Specific events	assistance with capillary glucose glucagon administration Other hypoglycaemia (HypoO) = measurement  Group 1 (n=91): Placebo + metfo	e <3.0mmol/L, recovery following glucose or esymptoms, but without confirmative or entire or esymptoms.	GTI = Genital Tract In: HypoS = Hypoglycaen HypoM = Hypoglycae HypoO = Hypoglycaen HypoT = Hypotension  Group 2 (n= 89): 10 n	fection mia (severe) 1 death in dapagliflozin group, no deaths i mia (mild) mia other No significant effect on bone formation an resorption or bone mineral density mg dapagliflozin + metformin				
Specific events	assistance with capillary glucose glucagon administration Other hypoglycaemia (HypoO) = measurement  Group 1 (n=91): Placebo + metfor UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO HypoT n=0	e <3.0mmol/L, recovery following glucose or symptoms, but without confirmative or symptoms.	GTI = Genital Tract In HypoS = Hypoglycaen HypoM = Hypoglycaen HypoO = Hypoglycaen HypoT = Hypotension  Group 2 (n= 89): 10 m  UTI n=6, GTI n=3 HypoM n=2, HypoS na HypoT n=1	fection mia (severe) 1 death in dapagliflozin group, no deaths i placebo group mia other No significant effect on bone formation an resorption or bone mineral density mg dapagliflozin + metformin  =0, HypoO n=0				
Specific events	assistance with capillary glucose glucagon administration  Other hypoglycaemia (HypoO) = measurement  Group 1 (n=91): Placebo + metform of the proof	e <3.0mmol/L, recovery following glucose or symptoms, but without confirmative or symptoms.	GTI = Genital Tract In HypoS = Hypoglycaen HypoM = Hypoglycaen HypoO = Hypoglycaen HypoT = Hypotension  Group 2 (n= 89): 10 m  UTI n=6, GTI n=3 HypoM n=2, HypoS na HypoT n=1 Events leading to disc	fection mia (severe) placebo group mia other n No significant effect on bone formation an resorption or bone mineral density mg dapagliflozin + metformin  1 death in dapagliflozin group, no deaths i placebo group no near new placebo group no new placebo gr				
Specific events	assistance with capillary glucose glucagon administration  Other hypoglycaemia (HypoO) = measurement  Group 1 (n=91): Placebo + metform of the measurement  UTI n=2, GTI n=0  HypoM n=2, HypoS n=0, HypoO  HypoT n=0  Events leading to discontinuation  Nasopharyngitis n=5	e <3.0mmol/L, recovery following glucose or symptoms, but without confirmative or symptoms.	GTI = Genital Tract In HypoS = Hypoglycaen HypoM = Hypoglycaen HypoO = Hypoglycaen HypoT = Hypotension  Group 2 (n= 89): 10 m  UTI n=6, GTI n=3 HypoM n=2, HypoS na HypoT n=1 Events leading to disconsistency	fection mia (severe) placebo group mia other n No significant effect on bone formation an resorption or bone mineral density mg dapagliflozin + metformin  1 death in dapagliflozin group, no deaths i placebo group no near new placebo group no new placebo gr				
Specific events	assistance with capillary glucose glucagon administration  Other hypoglycaemia (HypoO) = measurement  Group 1 (n=91): Placebo + metform of the proof	e <3.0mmol/L, recovery following glucose or symptoms, but without confirmative or symptoms.	GTI = Genital Tract In HypoS = Hypoglycaen HypoM = Hypoglycaen HypoO = Hypoglycaen HypoT = Hypotension  Group 2 (n= 89): 10 m  UTI n=6, GTI n=3 HypoM n=2, HypoS na HypoT n=1 Events leading to disc	fection mia (severe) placebo group mia other n No significant effect on bone formation an resorption or bone mineral density mg dapagliflozin + metformin  1 death in dapagliflozin group, no deaths i placebo group no near new placebo group no new placebo gr				
Specific events	assistance with capillary glucose glucagon administration  Other hypoglycaemia (HypoO) = measurement  Group 1 (n=91): Placebo + metform  UTI n=2, GTI n=0  HypoM n=2, HypoS n=0, HypoO  HypoT n=0  Events leading to discontinuation  Nasopharyngitis n=5  Hypertension n=4  Pneumonia n=0	e <3.0mmol/L, recovery following glucose or symptoms, but without confirmative or symptoms.	GTI = Genital Tract In HypoS = Hypoglycaen HypoM = Hypoglycaen HypoO = Hypoglycaen HypoT = Hypotension  Group 2 (n= 89): 10 m  UTI n=6, GTI n=3 HypoM n=2, HypoS n: HypoT n=1 Events leading to disc Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=3	fection mia (severe) placebo group mia other n No significant effect on bone formation an resorption or bone mineral density mg dapagliflozin + metformin  1 death in dapagliflozin group, no deaths i placebo group no near new placebo group no new placebo gr				
Specific events	assistance with capillary glucose glucagon administration  Other hypoglycaemia (HypoO) = measurement  Group 1 (n=91): Placebo + metform of the measurement  UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO HypoT n=0 Events leading to discontinuation Nasopharyngitis n=5 Hypertension n=4 Pneumonia n=0 Angina pectoris n=0	e <3.0mmol/L, recovery following glucose or symptoms, but without confirmative or symptoms.	GTI = Genital Tract In HypoS = Hypoglycaen HypoM = Hypoglycaen HypoO = Hypoglycaen HypoT = Hypotension  Group 2 (n= 89): 10 m  UTI n=6, GTI n=3 HypoM n=2, HypoS n: HypoT n=1 Events leading to disc Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=3 Angina pectoris n=2	fection mia (severe) placebo group mia other n No significant effect on bone formation an resorption or bone mineral density mg dapagliflozin + metformin  1 death in dapagliflozin group, no deaths i placebo group no near new placebo group no new placebo gr				
Specific events	assistance with capillary glucose glucagon administration  Other hypoglycaemia (HypoO) = measurement  Group 1 (n=91): Placebo + metform of the measurement  UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO HypoT n=0 Events leading to discontinuation Nasopharyngitis n=5 Hypertension n=4 Pneumonia n=0 Angina pectoris n=0 Cystitis n=1	e <3.0mmol/L, recovery following glucose or symptoms, but without confirmative or symptoms.	GTI = Genital Tract In HypoS = Hypoglycaen HypoM = Hypoglycaen HypoO = Hypoglycaen HypoT = Hypotension  Group 2 (n= 89): 10 m  UTI n=6, GTI n=3 HypoM n=2, HypoS n: HypoT n=1 Events leading to disc Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=3 Angina pectoris n=2 Cystitis n=2	fection mia (severe) placebo group mia other n No significant effect on bone formation an resorption or bone mineral density mg dapagliflozin + metformin  1 death in dapagliflozin group, no deaths i placebo group no near new placebo group no new placebo gr				
Specific events	assistance with capillary glucose glucagon administration  Other hypoglycaemia (HypoO) = measurement  Group 1 (n=91): Placebo + metform of the measurement  UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO HypoT n=0 Events leading to discontinuation Nasopharyngitis n=5 Hypertension n=4 Pneumonia n=0 Angina pectoris n=0	e <3.0mmol/L, recovery following glucose or symptoms, but without confirmative or symptoms.	GTI = Genital Tract In HypoS = Hypoglycaen HypoM = Hypoglycaen HypoO = Hypoglycaen HypoT = Hypotension  Group 2 (n= 89): 10 m  UTI n=6, GTI n=3 HypoM n=2, HypoS n: HypoT n=1 Events leading to disc Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=3 Angina pectoris n=2	fection mia (severe) placebo group mia other n No significant effect on bone formation an resorption or bone mineral density mg dapagliflozin + metformin  1 death in dapagliflozin group, no deaths in placebo group no near new placebo group no new placebo group				

type 2 diabetes wh	o have inadequate glycaemic control with metformin. Diabetes Care	e 2011; 34: 2015-2022 <sup>11</sup>	Bristol-Myers-Squibb						
			SGLT2 inhibitor (up to 10 mg						
			dapagliflozin) + metformin						
			versus metformin + glipizide						
	e efficacy, safety and tolerability of dapagliflozin with glipizide in pati	ients 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								
	<b>Duration of intervention</b> : 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	N: 801 analysed								
criteria	Inclusion criteria: participants aged 18 years and older; inadequately controlled type 2 diabetes (HbA1c >6.5 and ≤10%); BMI ≤45kg/m²; 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								
Intorvontions	1 0. 0								
Interventions	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose								
interventions	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg	g/day)							
interventions	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at each of the control of	g/day) enrolment 2000 mg/day); dapagliflozin started at 2	2.5 mg, up-titrated to maximum tolerable dose (up						
mterventions	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at 6 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolera	g/day) enrolment 2000 mg/day); dapagliflozin started at 2	2.5 mg, up-titrated to maximum tolerable dose (up						
interventions	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at 6 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolera All groups: diet and lifestyle advice	g/day) enrolment 2000 mg/day); dapagliflozin started at 2 able dose (up to 20 mg)							
	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at 6 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolera All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformi	g/day) enrolment 2000 mg/day); dapagliflozin started at 2 able dose (up to 20 mg) in stabilised to 1500 to 2000 mg/day; 2 weeks sing	gle blind placebo lead in prior to randomisation						
Participant	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at 6 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolera All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformic Group 1 (start n= 406, analysed n=400):	g/day) enrolment 2000 mg/day); dapagliflozin started at 2 able dose (up to 20 mg) in stabilised to 1500 to 2000 mg/day; 2 weeks sing Group 2 (start n= 408, analysed i	gle blind placebo lead in prior to randomisation						
	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at 6 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolera All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformic Group 1 (start n= 406, analysed n=400):  9.2 mg dapagliflozin + metformin	g/day) enrolment 2000 mg/day); dapagliflozin started at 2 sble dose (up to 20 mg) in stabilised to 1500 to 2000 mg/day; 2 weeks sing  Group 2 (start n= 408, analysed n 16.4 mg glipizide + metformin	gle blind placebo lead in prior to randomisation						
Participant	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at 6 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolera All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformi  Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years	g/day) enrolment 2000 mg/day); dapagliflozin started at 2 sble dose (up to 20 mg) in stabilised to 1500 to 2000 mg/day; 2 weeks sing  Group 2 (start n= 408, analysed n 16.4 mg glipizide + metformin  Age: 59 SD10 years	gle blind placebo lead in prior to randomisation						
Participant	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at 6 to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolera All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformi  Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years  Sex: 55.3% male	g/day) enrolment 2000 mg/day); dapagliflozin started at 2 sble dose (up to 20 mg) in stabilised to 1500 to 2000 mg/day; 2 weeks sing  Group 2 (start n= 408, analysed n 16.4 mg glipizide + metformin  Age: 59 SD10 years Sex: 54.9% male	gle blind placebo lead in prior to randomisation						
Participant	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at et to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolera All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformid Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years  Sex: 55.3% male  BMI (kg/m²): 31.7 SD5.1	g/day) enrolment 2000 mg/day); dapagliflozin started at 2 able dose (up to 20 mg) in stabilised to 1500 to 2000 mg/day; 2 weeks sing  Group 2 (start n= 408, analysed n 16.4 mg glipizide + metformin  Age: 59 SD10 years Sex: 54.9% male BMI (kg/m²): 31.2 SD5.1	gle blind placebo lead in prior to randomisation						
Participant	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at et to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolera All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformid Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years  Sex: 55.3% male  BMI (kg/m²): 31.7 SD5.1  ≥ 25 kg/m²: 95%	g/day) enrolment 2000 mg/day); dapagliflozin started at 2 able dose (up to 20 mg)  in stabilised to 1500 to 2000 mg/day; 2 weeks sing  Group 2 (start n= 408, analysed n 16.4 mg glipizide + metformin  Age: 59 SD10 years  Sex: 54.9% male  BMI (kg/m²): 31.2 SD5.1  ≥ 25 kg/m²: 90.8%	gle blind placebo lead in prior to randomisation						
Participant	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at et to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolera All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformid  Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years  Sex: 55.3% male  BMI (kg/m²): 31.7 SD5.1  ≥ 25 kg/m²: 95%  ≥ 30 kg/m²: 57%	g/day) enrolment 2000 mg/day); dapagliflozin started at 2 able dose (up to 20 mg)  in stabilised to 1500 to 2000 mg/day; 2 weeks sing  Group 2 (start n= 408, analysed in 16.4 mg glipizide + metformin  Age: 59 SD10 years  Sex: 54.9% male  BMI (kg/m²): 31.2 SD5.1  ≥ 25 kg/m²: 90.8%  ≥ 30 kg/m²: 55.4%	gle blind placebo lead in prior to randomisation						
Participant	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at et to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolera All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformid  Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years  Sex: 55.3% male  BMI (kg/m²): 31.7 SD5.1  ≥ 25 kg/m²: 95%  ≥ 30 kg/m²: 57%  HbA1c (%): 7.7% SD0.9	g/day) enrolment 2000 mg/day); dapagliflozin started at 2 able dose (up to 20 mg)  in stabilised to 1500 to 2000 mg/day; 2 weeks sing  Group 2 (start n= 408, analysed n 16.4 mg glipizide + metformin  Age: 59 SD10 years  Sex: 54.9% male  BMI (kg/m²): 31.2 SD5.1  ≥ 25 kg/m²: 90.8%  ≥ 30 kg/m²: 55.4%  HbA1c (%): 7.7% SD0.9	gle blind placebo lead in prior to randomisation n= 401):						
Participant	Intervention 1: dapagliflozin + metformin (dapagliflozin mean dose Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg OAD schedule: metformin 1500 to 2000 mg/day (median dose at et to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolera All groups: diet and lifestyle advice  Lead in period: before lead in: other OADs discontinued, metformid  Group 1 (start n= 406, analysed n=400): 9.2 mg dapagliflozin + metformin  Age: 58 SD9 years  Sex: 55.3% male  BMI (kg/m²): 31.7 SD5.1  ≥ 25 kg/m²: 95%  ≥ 30 kg/m²: 57%	g/day) enrolment 2000 mg/day); dapagliflozin started at 2 able dose (up to 20 mg)  in stabilised to 1500 to 2000 mg/day; 2 weeks sing  Group 2 (start n= 408, analysed in 16.4 mg glipizide + metformin  Age: 59 SD10 years  Sex: 54.9% male  BMI (kg/m²): 31.2 SD5.1  ≥ 25 kg/m²: 90.8%  ≥ 30 kg/m²: 55.4%	gle blind placebo lead in prior to randomisation n= 401):						

	Group 1 (n=400): 9.2 mg da	apagliflozin + metformin	Group 2 (n= 401): 16.4 mg glipizide + m	etformin		
	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	s (MedDRA v12.1) via patient questionnaire a	nd active questioning during visits		
	Severe hypoglycaemia (Hy	poS) = symptomatic episode, needing external	General events – where frequency is	At least one or more adverse event		
	assistance with following re	ecovery, capillary glucose <3.0mmol/L	≥3%	<b>Group 1 =</b> n=318		
	Minor hypoglycaemia (Hyp	ooM) = symptomatic episode, capillary glucose	UTI = Urinary Tract Infection	<b>Group 2 =</b> n=318		
	<3.5mmol/L		GTI = Genital Tract Infection			
	Other hypoglycaemia (Hyp	oO) = symptoms, but without measurement	HypoS = Hypoglycaemia (severe)	No deaths in dapagliflozin group		
	confirming		HypoM = Hypoglycaemia (mild)	3 deaths in glipizide group		
			HypoO = Hypoglycaemia other	ypoO = Hypoglycaemia other		
			HypoT = Hypotension			
	Group 1 (n=406): 9.2 mg da	apagliflozin + metformin	Group 2 (n= 408): 16.4 mg glipizide + m	etformin		
Specific events	UTI n=44, GTI n=50		UTI n=26, GTI n=11			
	HypoS n=0, HypoM n=7, Hy	vpoO n=7	HypoS n=3, HypoM n=147, HypoO n=40			
	HypoT n=6		HypoT n=3			
	Renal impairment / failure	n=24	Renal impairment / failure n=14 Events leading to discontinuation n=24 (6 due to hypoglycaemia)			
	Events leading to discontin	uation n=37 (0 due to hypoglycaemia)				
	Diarrhoea n=19		Diarrhoea n=26			
	Nausea n=14		Nausea n=15			
	Vulvovaginal mycotic infect	tion n=14	Vulvovaginal mycotic infection n=2			
	Back pain n=19		Back pain n=20	<i>5</i> ,		
	Nasopharyngitis n= 43		Nasopharyngitis n=61			
	Cough n=15		Cough n=20	. , ,		
	Influenza n=30		Influenza n=30			
	Arthralgia n=11		Arthralgia n=21			
	Upper resp. tract Infection	n=24	Upper resp. tract Infection n=31			
	Headache n=21		Headache n=17			
	Hypertension n=30		Hypertension n=35			

	M, Wei L, Salsali A, List JF. <b>Effects of dapagliflozin, an SG</b> <b>2 diabetes inadequately controlled in pioglitazone mo</b> i	LT2 inhibitor, on HbA1c, body weight, and hypoglycaemic notherapy. Diabetes Care 2012; 35: 1473-1478 <sup>12</sup>	a risk in Funding source: Astra-Zeneca and Bristol-Myers-Squibb
			SGLT2 inhibitor (5 or 10 mg dapagliflozin) + pioglitazone versus placebo + pioglitazone
		ne in type 2 diabetes patients inadequately controlled on p	<mark>pioglitazone</mark>
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, place		
	Primary outcome: change from baseline in HbA1c at	week 24	
	Secondary outcomes:		
	At week 24, change from baseline in:		
	- Fasting plasma glucose		
	<ul> <li>Postprandial glucose</li> </ul>		
	- Total body weight		
	- Blood pressure		
	<ul> <li>Adverse events, laboratory values, vital signs</li> </ul>		
Participant Participant	N: 420 analysed		2
<mark>criteria</mark>		ge ≥18 years; fasting C-peptide ≥1.0 ng/mL; BMI ≤45 kg/m	
		revious 10 weeks with HbA1c ≥8.0 to ≤11.0% or had receive	
		s of metformin ≤1700 mg/day or sulphonylurea ≤half maxi	
		week dose optimisation in which initial therapy was discont	itinued and pioglitazone 30 mg/day was started and
	increased to 45 mg/day if possible; pre-randomisatio		
		of normal; total bilirubin >2.0 mg/dL, serum creatinine ≥2.0	o mg/dL, urine albumin/creatinine ratio >1800 mg/g,
	calculated creatinine clearance <50 mL/min, congesti	ve neart failure class ill and iv	
<b>Interventions</b>	Intervention 1: 5 mg dapagliflozin + pioglitazone		
	Intervention 2: 10 mg dapagliflozin + pioglitazone Intervention 3: placebo + pioglitazone		
		day; dapagliflozin once daily; in case of inadequate glycaem	oic control (EDC >270 mg/dL (wook 4 to 9) or > 240 mg/dL
		is were eligible for open label rescue medication (metform	
	All groups: diet and exercise counselling	.s were eligible for open laber rescue medication (metiorm	ini or sulphonylurea;
	Lead in period: 2 weeks, single blind, placebo lead in		
Participant	Group 1 (n=139): Placebo + pioglitazone	Group 2 (n=141): 5 mg dapagliflozin + pioglitazone	Group 2 (n=140): 10 mg dapagliflozin + pioglitazone
baseline data	<b>Age:</b> 53.5 SD11.4 years	Age: 53.2 SD10.9 years	Age: 53.8 SD10.2 years
vaseiiile uata	<b>Sex:</b> 51.1% male	Sex: 55.3% male	Sex: 42.1% male
	<b>BMI:</b> $61.2\% \ge 30 \text{ kg/m}^2$ ; $87.8\% \ge 25 \text{ kg/m}^2$	<b>BMI:</b> 61.7% ≥30 kg/m <sup>2</sup> ; 86.5% ≥25 kg/m <sup>2</sup>	<b>BMI:</b> 51.4% ≥30 kg/m <sup>2</sup> ; 92.9% ≥25 kg/m <sup>2</sup>
	HbA1c: 8.34% SD1.00	HbA1c: 8.40% SD1.03	HbA1c: 8.37% SD0.96
	<b>Duration of diabetes:</b> 5.07 SD5.05 years	Duration of diabetes: 5.64 SD5.36 years	Duration of diabetes: 5.75 SD6.44 years
	Duration of diabetes. 3.07 3D3.03 years	Duration of diabetes. 3.04 3D3.30 years	Duration of diabetes. 3.73 300.44 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	o + pioglitazone	Group 2 (n=141): 5 mg dapagliflozin + pioglitazone			(n=140): 10 mg dapagliflozin + pioglitazone		
	<mark>Mean</mark>	<mark>SE</mark>	<mark>Mean</mark>		<b>Mean</b>	<mark>SE</mark>		
ΔHbA1c (%)	wk 24: -0.42	<mark>0.08</mark>	<mark>-0.82</mark>	0.08, p=0.0007 vs placebo	<mark>-0.97</mark>	0.08, p<0.0001 vs placebo		
	wk 48: -0.54	<mark>0.08</mark>	<mark>-0.95</mark>	0.08, p NR	<mark>-1.21</mark>	0.07, p NR		
<mark>ΔWeight (kg)</mark>	wk 24: +1.64	<mark>0.28</mark>	+0.09	0.28, p<0.0001 vs placebo	<mark>-0.14</mark>	0.28, p<0.0001 vs placebo		
	wk 48: +2.99	<mark>0.41</mark>	+1.35	0.38, p NR	+0.69	0.36, p NR		
ΔFPG (mmol/L)	wk 24: -0.31	<mark>0.16</mark>	<mark>-1.38</mark>	0.16, p<0.0001 vs placebo	<mark>-1.64</mark>	0.16, p<0.0001 vs placebo		
	wk 48: -0.73	<mark>0.20</mark>	<mark>-1.27</mark>	0.18, p NR	<mark>-1.84</mark>	0.17, p NR		
ΔSBP (mmHg)	wk 24: +1.3	1.2	<mark>-0.8</mark>	1.2, p NS	<mark>-3.4</mark>	1.2, p NS		
	wk 48: +2.0	<mark>1.2</mark>	<mark>-1.0</mark>	1.1, p NR	<mark>-2.2</mark>	<mark>0.7, p NR</mark>		
Adverse events								
Safety assessment	t: assessed at every visit, que	estioning, laboratory tests an	<mark>d vital signs</mark>					
		lypoM) = symptomatic episoo		the state of the s		least one or more adverse event		
		tic episode with glucose <3.5		frequency is >5%	<b>Group 1 = 66.9%</b>			
		HypoS) = symptomatic episod				<mark>oup <b>2 =</b> 68.1%</mark>		
		<mark>glucose &lt;3.0mmol/L, recove</mark> i	ry following glucose or	GTI = Genital Tract Infection		<mark>oup 3 = 70.7%</mark>		
	glucagon administration			HypoS = Hypoglycaemia (sever				
		ypoO) = symptoms, but with	out confirmative	HypoM = Hypoglycaemia (milo				
	measurement			HypoO = Hypoglycaemia other				
	Group 1 (n=139): Placebo	o + pioglitazone		dapagliflozin + pioglitazone		(n=140): 10 mg dapagliflozin + pioglitazone		
Specific events	UTI n=11, GTI n=4		UTI n=12, GTI n=13		- ,	<mark>, GTI n=12</mark>		
	Any hypoglycaemia n=1,		Any hypoglycaemia n=3,			oglycaemia n=0, HypoS n=0		
	Decreased renal function		Decreased renal function		Decreased renal function n=2			
	Events leading to discont	inuation n=5	Events leading to discon	tinuation n=5		eading to discontinuation n=3		
	Dyslipidaemia n=9		Dyslipidaemia n=11		, ,	<mark>aemia n=16</mark>		
	Nasopharyngitis n=7		Nasopharyngitis n=7			<mark>aryngi</mark> tis n=11		
	Diarrhoea n=6		Diarrhoea n=5		Diarrhoe			
	Back pain n=4		Back pain n=5		Back pai			
	Upper resp. tract infection	on n=10	Upper resp. tract infecti	on n=10		esp. tract infection n=7		
	Headache n=10		Headache n=3		Headache n=4			
	Pain in extremity n=1		Pain in extremity n=10			extremity n=4		
	Oedema peripheral n=9		Oedema peripheral n=6		Oedema	<mark>a peripheral n=3</mark>		

		th S. <b>Effect of Dapagliflozin in patients with ty</b> Il <b>e-blind, placebo-controlled trial.</b> Diabetes, Ob								
				versus placebo plus glimepiride						
 <b>Δim:</b> to determi	ine the efficacy, safety and tolerability of	dapagliflozin treatment, as an add-on therapy	to glimeniride in natients with inadequately							
	phonylurea monotherapy	dapagiiioziii treatiiieiit, as aii add oii tiierapy	to girriepiriae, in patients with inadequatery	controlled type 2 diabetes who had bee						
Study quality	High – see quality table for further inf	ormation								
Study quality Study	Multi-centre: 84 sites across 7 countr									
particulars	Duration of intervention: 24 weeks	ics world-wide								
our cicular s	Duration of run in: 1 week for patient	s switched to alimenicide								
	Follow-up: on completion of 24 week									
	<b>Design:</b> 4-arm parallel group RCT, dou									
	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/m²									
	- Change in FPG									
Participant	N: 592 analysed		_							
criteria		Byears and older; inadequately controlled type		/m²; 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 me	dication 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;									
	1 ' = '	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/m² received advice about reducing caloric intake and increasing physical activity								
	1 - ' '		<del>-</del>	ric intake and increasing physical activi						
		exclusion review for those switched to 4 mg/da								
Participant	Group 1 (n= 146)	Group 2 (n= 154)	Group 3 (n= 145)	Group 4 (n= 151)						
oaseline data	Placebo + glimepiride	2.5 mg dapagliflozin + glimepiride	5 mg dapagliflozin + glimepiride	10 mg dapagliflozin + glimepiride						
	<b>Age:</b> 60.3 SD10.16 years	<b>Age:</b> 59.9 SD10.14 years	<b>Age:</b> 60.2 SD 9.73 years	<b>Age:</b> 58.9 SD 8.32 years						
	<b>Sex:</b> 49% male <b>BMI:</b> 86.2% ≥25 kg/m <sup>2</sup> ; 45.5% ≥30	Sex: 50% male BMI: 84.4% ≥25 kg/m <sup>2</sup> ; 48.1% ≥30 kg/m <sup>2</sup>	<b>Sex:</b> 50% male <b>BMI:</b> 80.3% ≥25 kg/m <sup>2</sup> ; 51.4% ≥30 kg/m <sup>2</sup>	<b>Sex:</b> 43.7% male <b>BMI:</b> 79.5% ≥25 kg/m <sup>2</sup> ; 45% ≥30 kg/m						

	kg/m <sup>2</sup> HbA		<b>HbA1c:</b> 8.11% SD0.75		<b>HbA1c:</b> 8.12% SD0.78		HbA1c: 8.0	)7% SD0.79
	<b>HbA1c:</b> 8.15% SD0.74 <b>D</b> 6		<b>Duration of diabetes:</b> 7.7 SD6.0 years		Duration of diabetes: 7.4 SD5.7 years		<b>Duration of diabetes:</b> 7.2 SD5.5 years	
	Duration of di	abetes: 7.4 SD5.7 years	FPG (mmol/L): 9.56 SD2.13		FPG (mmol/L): 9.68 SD2.12		FPG (mmol/L): 9.55 SD2.04	
	FPG (mmol/L)	: 9.58 SD2.07	Systolic BP	(mmHg): 134.6	Systolic BP	(mmHg): 130.9	Systolic BP	(mmHg): 132.4
	Systolic BP (m	mHg): 133.3						
Outcome (chang	ge from baseline	to study end (week 24))						
	Group 1 (n= 14	46)	Group 2 (n=	: 154)	Group 3 (n=	= 145)	Group 4 (n	= 151)
	Placebo + glim	epiride	2.5 mg dapagliflozin + glimepiride		5 mg dapagliflozin + glimepiride		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],	-0.63	-0.76 to -0.5 [from graph],	-0.82	-0.94 to -0.7 [from graph],
				p<0.0001 vs placebo		p<0.0001 vs placebo		p<0.0001 vs placebo
ΔWeight (kg)	-0.72	-0.96 to -0.48 [from	-1.18	-1.42 to -0.94 [from graph],	-1.56	-1.8 to -1.32 [from graph],	-2.26	-2.5 to -2.02 [from graph],
		graph]		NS		p<0.0091 vs placebo		p<0.0001 vs placebo
ΔFPG	-0.11	-	-0.93	-	-1.18	-	-1.58	-
(mmol/L)								
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
ΔSBP (mmHg)	-1.20	-	-4.7	-9	-4.0	-	-5.0	-
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; hypoglycaemic events, laboratory testing, vital signs

	Hypoglycaemia not clearly defined		General events – where frequency is	At least one or more adverse event
			≥3% in any group	<b>Group 1 =</b> n=69; <b>Group 2 =</b> n=80
			UTI = Urinary Tract Infection	<b>Group 3 =</b> n=70; <b>Group 4 =</b> n=76
			GTI = Genital Tract Infection	
			Hypo = Hypoglycaemia	1 death in dapagliflozin 2.5 mg
				1 death in dapagliflozin 10 mg
	Group 1 (n= 146)	Group 2 (n= 154)	Group 3 (n= 145)	Group 4 (n= 151)
	Placebo + glimepiride	2.5 mg dapagliflozin + glimepiride	5 mg dapagliflozin + glimepiride	10 mg dapagliflozin + glimepiride
Specific events	UTI n=9, GTI n= 1	UTI n=6, GTI n=6	UTI n=10, GTI n=9	UTI n=8, GTI n=10
	≥ 1 Hypo n=7	≥ 1 Hypo n=11	≥ 1 Hypo n=10	≥ 1 Hypo n=12
	Renal impairment / failure n=2	Renal impairment / failure n=1	Renal impairment / failure n=1	Renal impairment / failure n=0
	Events leading to discontinuation n=3	Events leading to discontinuation n=5	Events leading to discontinuation n=5	Events leading to discontinuation n=4
	Bronchitis n=1	Bronchitis n=2	Bronchitis n=3	Bronchitis n=5
	Diarrhoea n=5	Diarrhoea n=4	Diarrhoea n=2	Diarrhoea n=0
	Back pain n= 4	Back pain n=3	Back pain n=3	Back pain n=7
	Nasopharyngitis n=4	Nasopharyngitis n=3	Nasopharyngitis n=8	Nasopharyngitis n=5
	Arthralgia n=4	Arthralgia n=6	Arthralgia n=0	Arthralgia n=1
	Upper resp. tract Infection n=4	Upper resp. tract Infection n=5	Upper resp. tract Infection n=6	Upper resp. tract Infection n=7
	Hypertension n=6	Hypertension n=8	Hypertension n=2	Hypertension n=2

	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	N: 71 analysed							
criteria	Inclusion criteria: participants aged between 18 and 75 years; type 2 diabetes; BMI ≤45 kg/m²; 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	Group 1 (n=23): Placebo	+ OAD + insulin	Group 2 (n= 24): 1	10 mg dapagliflozin + OAD + insulin	Group 3 (n= 24): 20 mg dapagliflozin + OAD + insulin		
baseline data	<b>Age:</b> 58.4 SD6.5 years		<b>Age:</b> 55.7 SD9.2 y	ears	<b>Age:</b> 56.1 SD10.6 years <b>Sex:</b> 54.2% male		
	<b>Sex:</b> 69.6% male		<b>Sex:</b> 54.2% male				
	<b>BMI (kg/m²):</b> 34.8 SD4.6	5	BMI (kg/m <sup>2</sup> ): 35.5	5 SD3.6	BMI (kg/m <sup>2</sup> ): 36.	2 SD4.6	
	<b>HbA1c:</b> 8.40% SD0.9		HbA1c: 8.4% SD0.	.7	HbA1c: 8.5% SD0	0.9	
	Duration of diabetes: 13	3.8 SD 7.3 years	Duration of diabe	etes: 11.8 SD5.8 years	Duration of diab	<b>etes:</b> 11.3 SD5.6 years	
	FPG (mmol/L): 9.22 SD 2	2.86	FPG (mmol/L): 8.6	67 SD 2.17	FPG (mmol/L): 8.	.98 SD 3.06	
	Systolic BP (mmHg): NR		Systolic BP (mmH	lg): NR	Systolic BP (mml	lg): NR	
Outcome (change	from baseline at study end	(week 12))					
	Group 1 (n=23): Placebo	+ OAD + insulin	Group 2 (n= 24): 1	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	t: treatment-emergent adve	erse events, vital signs, laborato	ory measurements				
	Minor hypoglycaemia =	symptomatic episode,	General events – where frequency is >5%		At least one or more adverse event		
	capillary glucose <3.5mr	nol/L	UTI = Urinary Trac	ct Infection	Group 1 = n=15 Group 2 = n=18 Group 3 = n=16		
	Major hypoglycaemia =	symptomatic episode,	GTI = Genital Trac	t Infection			
	needing external assista	nce with following recovery,	HypoT = Hypotens	sion, HypoG = Hypoglycaemia			
	capillary glucose <3.0mr	mol/L	HypoS = major hy	poglycaemia			
	Group 1 (n=23): Placebo	+ OAD + insulin	Group 2 (n= 24): 1	10 mg dapagliflozin + OAD + insulin	Group 3 (n= 24): 20 mg dapagliflozin + OAD + insulir		
Specific events	UTI n=0, GTI n = 1		UTI n= 0, GTI n = 0	0	UTI n= 1, GTI n = 5		
	HypoT n=NR, HypoG n=3	3, HypoS n=1	HypoT n=NR, Hyp	oG n=7, HypoS n=0	HypoT n=NR, HypoG n=6, HypoS n=0		
	Events leading to discon	tinuation n=1	Events leading to	discontinuation n=1	Events leading to discontinuation n=1		
	Nausea n=1		Nausea n=1		Nausea n=3		
	Pollakiuria n=4		Pollakiuria n=2		Pollakiuria n=3		
	Back pain n=2		Back pain n=3		Vomiting n=3		
	Nasopharyngitis n=2		Nasopharyngitis n	n=2	Vulvovaginal mycotic infection n=3		
	Upper abdominal pain n	= 2	Fatigue n=2		Anxiety n=2		
	Influenza n=2		Influenza n=1		Back pain n=2		
	Pain in extremity n=1		Pain in extremity		Dry Mouth n=2		
	Upper resp. tract Infecti	on n=2	Upper resp. tract	Infection n=2	Nasopharyngitis n=2		
	Headache n= 2		Headache n=3		Peripheral oeden		
	Procedural pain n=2		Pharyngolaryngea	al pain n=2	Upper abdomina	l pain n=1	
					Fatigue n=1		
					Influenza n=1		
					Pain in extremity n=1		

			Upper resp.	tract Infection n=1							
		edder K, Parikh S. Long-term efficacy of dapaglif									
eceiving high	doses of insulin. A randomized trial. A	nnals of Internal Medicine 2012; 156(6): 405-41	5 <sup>15</sup>	Bristol-Myers-Squibb							
				SGLT2 Inhibitor (2.5, 5 or 10 mg							
				dapagliflozin) + insulin ± OAD							
				versus placebo + insulin ± OAD							
		pagliflozin to patients whose type 2 diabetes is in	nadequately controlled with insulin with or with	out oral antidiabetic drugs							
tudy quality	High – see quality table for further i	<mark>nformation</mark>									
<mark>itudy</mark>	Multi-centre: 126 worldwide										
oarticulars											
	Duration of run in: 2 week enrolme										
		eks, 24 week extension plus further 56 week exte	ension 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										
		ts, vital signs									
Participant	N: 800 analysed	10 100 100 100 100 100 100 100 100 100	.45   / 2	4 > 7 5 + 440 50() + 11 + 11 + 11							
<mark>criteria</mark>		between 18 and 80 years; type 2 diabetes; BMI									
		8 weeks; additional treatment with up to two OA	ADS allowed (≥1500 mg metformin or maximun	i tolerated dose or at least half maximu							
	dose of other OADS for ≥8 weeks)										
	receiving metformin >133 µmol/L for	signs of poorly controlled diabetes; calculated cro	eatinine clearance <50 mi/min per 1.73 m or s	erum creatinine ≥177 µmoi/L, or if							
	Intervention 1: placebo + insulin ± OAD										
nterventions <b></b>											
nterventions	Intervention 2: 2.5 mg dapagliflozin	+ insulin ± OAD									
nterventions	Intervention 2: 2.5 mg dapagliflozin Intervention 3: 5 mg dapagliflozin +	+ insulin ± OAD insulin ± OAD									
nterventions	Intervention 2: 2.5 mg dapagliflozin Intervention 3: 5 mg dapagliflozin + Intervention 4: 10 mg dapagliflozin	+ insulin ± OAD insulin ± OAD + insulin ± OAD	by dose of insulin (man daily dose 77.1.11) and	evicting OADs (none in ~50% metform							
nterventions	Intervention 2: 2.5 mg dapagliflozin Intervention 3: 5 mg dapagliflozin + Intervention 4: 10 mg dapagliflozin OAD/insulin schedule: dapagliflozin	+ insulin ± OAD insulin ± OAD + insulin ± OAD once daily; open label treatment with usual dail									
nterventions	Intervention 2: 2.5 mg dapagliflozin Intervention 3: 5 mg dapagliflozin + Intervention 4: 10 mg dapagliflozin OAD/insulin schedule: dapagliflozin only in ~40%, metformin in combina	+ insulin ± OAD insulin ± OAD + insulin ± OAD once daily; open label treatment with usual dail tion in ~5 to 8%, other OAD / combination in ~1									
nterventions	Intervention 2: 2.5 mg dapagliflozin Intervention 3: 5 mg dapagliflozin Intervention 4: 10 mg dapagliflozin OAD/insulin schedule: dapagliflozin only in ~40%, metformin in combinate could be up-or down-titrated if need	+ insulin ± OAD insulin ± OAD + insulin ± OAD once daily; open label treatment with usual dail ation in ~5 to 8%, other OAD / combination in ~1 ded	.5 to 6%); OAD doses could be decreased when								
	Intervention 2: 2.5 mg dapagliflozin Intervention 3: 5 mg dapagliflozin + Intervention 4: 10 mg dapagliflozin OAD/insulin schedule: dapagliflozin only in ~40%, metformin in combina could be up-or down-titrated if need All groups: instructed to follow stab	+ insulin ± OAD insulin ± OAD + insulin ± OAD t insulin ± OAD conce daily; open label treatment with usual dail ation in ~5 to 8%, other OAD / combination in ~1 ded le diet and exercise regimen; <b>Lead in period:</b> un	.5 to 6%); OAD doses could be decreased when clear	hypoglycaemia was a concern; insulin							
<sup>p</sup> articipant	Intervention 2: 2.5 mg dapagliflozin Intervention 3: 5 mg dapagliflozin Intervention 4: 10 mg dapagliflozin OAD/insulin schedule: dapagliflozin only in ~40%, metformin in combinate could be up-or down-titrated if need All groups: instructed to follow stab Group 1 (n analysed=193):	+ insulin ± OAD insulin ± OAD + insulin ± OAD to once daily; open label treatment with usual dail ation in ~5 to 8%, other OAD / combination in ~1 ded le diet and exercise regimen; Lead in period: une Group 2 (n=202):	.5 to 6%); OAD doses could be decreased when clear Group 3 (n=211):	hypoglycaemia was a concern; insulin  Group 4 (n=194):							
<sup>p</sup> articipant	Intervention 2: 2.5 mg dapagliflozin Intervention 3: 5 mg dapagliflozin Intervention 4: 10 mg dapagliflozin OAD/insulin schedule: dapagliflozin only in ~40%, metformin in combinational be up-or down-titrated if need All groups: instructed to follow stab Group 1 (n analysed=193): Placebo + insulin ± OAD	+ insulin ± OAD insulin ± OAD + insulin ± OAD once daily; open label treatment with usual dail ation in ~5 to 8%, other OAD / combination in ~1 ded le diet and exercise regimen; Lead in period: und Group 2 (n=202): 2.5 mg dapagliflozin + insulin ± OAD	.5 to 6%); OAD doses could be decreased when clear  Group 3 (n=211): 5 mg dapagliflozin + insulin ± OAD	hypoglycaemia was a concern; insulin  Group 4 (n=194):  10 mg dapagliflozin + insulin ± OAD							
Participant	Intervention 2: 2.5 mg dapagliflozin Intervention 3: 5 mg dapagliflozin Intervention 4: 10 mg dapagliflozin OAD/insulin schedule: dapagliflozin only in ~40%, metformin in combinational could be up-or down-titrated if need All groups: instructed to follow stab Group 1 (n analysed=193): Placebo + insulin ± OAD Age: 58.8 SD8.6 years	+ insulin ± OAD insulin ± OAD + insulin ± OAD  once daily; open label treatment with usual dail ation in ~5 to 8%, other OAD / combination in ~1  ded le diet and exercise regimen; Lead in period: und  Group 2 (n=202):  2.5 mg dapagliflozin + insulin ± OAD  Age: 59.8 SD7.6 years	.5 to 6%); OAD doses could be decreased when clear  Group 3 (n=211): 5 mg dapagliflozin + insulin ± OAD  Age: 59.3 SD7.9 years	hypoglycaemia was a concern; insulin  Group 4 (n=194):  10 mg dapagliflozin + insulin ± OAD  Age: 59.3 SD8.8 years							
Participant	Intervention 2: 2.5 mg dapagliflozin Intervention 3: 5 mg dapagliflozin Intervention 4: 10 mg dapagliflozin Hintervention 4: 10 mg dapagliflozin OAD/insulin schedule: dapagliflozin only in ~40%, metformin in combinational could be up-or down-titrated if need All groups: instructed to follow stab Group 1 (n analysed=193): Placebo + insulin ± OAD Age: 58.8 SD8.6 years Sex: 49.2% male	+ insulin ± OAD insulin ± OAD + insulin ± OAD nonce daily; open label treatment with usual dail ation in ~5 to 8%, other OAD / combination in ~1 ded le diet and exercise regimen; Lead in period: und Group 2 (n=202): 2.5 mg dapagliflozin + insulin ± OAD Age: 59.8 SD7.6 years Sex: 49.5% male	.5 to 6%); OAD doses could be decreased when clear  Group 3 (n=211): 5 mg dapagliflozin + insulin ± OAD  Age: 59.3 SD7.9 years Sex: 47.4% male	hypoglycaemia was a concern; insulin  Group 4 (n=194):  10 mg dapagliflozin + insulin ± OAD  Age: 59.3 SD8.8 years  Sex: 44.8% male							
Interventions Participant baseline data	Intervention 2: 2.5 mg dapagliflozin Intervention 3: 5 mg dapagliflozin Intervention 4: 10 mg dapagliflozin OAD/insulin schedule: dapagliflozin only in ~40%, metformin in combinate could be up-or down-titrated if need All groups: instructed to follow stable Group 1 (n analysed=193): Placebo + insulin ± OAD  Age: 58.8 SD8.6 years  Sex: 49.2% male BMI (kg/m²): 33.1 SD5.9	+ insulin ± OAD insulin ± OAD + insulin ± OAD nonce daily; open label treatment with usual dail ation in ~5 to 8%, other OAD / combination in ~1 ded le diet and exercise regimen; Lead in period: und Group 2 (n=202): 2.5 mg dapagliflozin + insulin ± OAD Age: 59.8 SD7.6 years Sex: 49.5% male BMI (kg/m²): 33.0 SD5.0	clear  Group 3 (n=211): 5 mg dapagliflozin + insulin ± OAD  Age: 59.3 SD7.9 years Sex: 47.4% male BMI (kg/m²): 33.0 SD5.3	hypoglycaemia was a concern; insulin  Group 4 (n=194): 10 mg dapagliflozin + insulin ± OAD  Age: 59.3 SD8.8 years  Sex: 44.8% male  BMI (kg/m²): 33.4 SD5.1							
Participant .	Intervention 2: 2.5 mg dapagliflozin Intervention 3: 5 mg dapagliflozin Intervention 4: 10 mg dapagliflozin Hintervention 4: 10 mg dapagliflozin OAD/insulin schedule: dapagliflozin only in ~40%, metformin in combinational could be up-or down-titrated if need All groups: instructed to follow stab Group 1 (n analysed=193): Placebo + insulin ± OAD Age: 58.8 SD8.6 years Sex: 49.2% male	+ insulin ± OAD insulin ± OAD + insulin ± OAD nonce daily; open label treatment with usual dail ation in ~5 to 8%, other OAD / combination in ~1 ded le diet and exercise regimen; Lead in period: und Group 2 (n=202): 2.5 mg dapagliflozin + insulin ± OAD Age: 59.8 SD7.6 years Sex: 49.5% male BMI (kg/m²): 33.0 SD5.0 HbA1c (%): 8.46% SD0.78	.5 to 6%); OAD doses could be decreased when clear  Group 3 (n=211): 5 mg dapagliflozin + insulin ± OAD  Age: 59.3 SD7.9 years Sex: 47.4% male	hypoglycaemia was a concern; insulin  Group 4 (n=194):  10 mg dapagliflozin + insulin ± OAD  Age: 59.3 SD8.8 years  Sex: 44.8% male							

	Systolic BP (mn	nHg): 136.1 SD17.2	Systolic BP (r	mmHg): 139.6 SD17.7	Systolic B	P (mmHg): 137.8 SD16.2	Systolic BP (	Systolic BP (mmHg): 140.6 SD16.7		
Outcome (chang										
	Group 1 (n ana		Group 2 (n=2		Group 3 (			Group 4 (n=194):		
	<mark>Placebo + insuli</mark>		2.5 mg dapag	gliflozin + insulin ± OAD	5 mg dapa	agliflozin + insulin ± OAD	10 mg dapagliflozin + insulin ± OAD			
	<mark>Mean</mark>	95% CI	<b>Mean</b>	95% CI	<mark>Mean</mark>	95% CI	<b>Mean</b>	95% CI		
<mark>ΔΗbΑ1c (%)</mark>	wk 24: -0.39	-0.5 to -0.28 [graph]	<mark>-0.79</mark>	-0.89 to -0.69 [graph]	<mark>-0.89</mark>	-0.99 to -0.79	<mark>-0.96</mark>	<mark>-1.06 to -0.86</mark>		
	wk 48: -0.47	-0.59 to -0.35 [graph]	<mark>-0.79</mark>	-0.9 to -0.68 [graph]	<mark>-0.96</mark>	-1.07 to -0.85	<mark>-1.01</mark>	<mark>-1.12 to -0.9</mark>		
				P<0.0001 vs placebo		p<0.0001 vs placebo		p<0.0001 vs placeb		
<mark>ΔWeight (kg)</mark>	wk 24: 0.43	0.05 to 0.81 [graph]	<mark>-0.92</mark>	-1.29 to -0.55	<mark>-1.0</mark>	-1.37 to -0.63	<mark>-1.61</mark>	<mark>-1.98 to -1.24</mark>		
	<mark>wk 48: 0.82</mark>	0.29 to 1.35 [graph]	<mark>-0.96</mark>	-1.48 to -0.44	<mark>-1.0</mark>	<mark>-1.52 to -0.48</mark>	<mark>-1.61</mark>	<mark>-2.14 to -1.08</mark>		
				p<0.0001 vs placebo		p<0.0001 vs placebo		p<0.0001 vs placeb		
<mark>ΔFPG</mark>	<i>wk 24:</i> NR		<mark>-0.65</mark>	-1.19 to -0.11, p NR	<mark>-1.12</mark>	-1.66 to -0.59, p NR	<mark>-1.10</mark>	-1.64 to -0.56. p NF		
(mmol/L)	<u>wk 48: NR</u>		<mark>-0.69</mark>	-1.28 to -0.11, p NR	<mark>-0.90</mark>	-1.48 to -0.33, p NR	<mark>-0.94</mark>	-1.53 to -0.36, p NF		
				p<0.0001 vs placebo		p<0.0001 vs placebo		p<0.0001 vs placeb		
ΔSBP (mmHg)	wk 24: -3.56	-5.47 to -1.64	<mark>-4.21</mark>	-6.05 to -2.38, p NR	<mark>-5.93</mark>	-7.74 to -4.12, p NR	<mark>-6.66</mark>	-8.53 to -4.80, p NF		
	wk 48: -1.49	-3.55 to 0.57	<mark>-5.70</mark>	-7.25 to -3.34, p NR	<mark>-4.33</mark>	-6.28 to -2.38, p NR	<mark>-4.09</mark>	<mark>-6.09 to -2.09, p NF</mark>		
Adverse events										
Safety assessme		nts, laboratory values, vital								
		<mark>/caemia =</mark> symptomatic epi			<mark>General e</mark>	vents – where frequency is	At least one	At least one or more adverse event		
		<mark>/caemia =</mark> symptomatic epi		external assistance with	<mark>≥5%</mark>		Group 1 = n=	Group 1 = n=144		
		very, capillary glucose <3.0				nary Tract Infection		<b>Group 2 =</b> n=153		
	Other hypogly	<mark>rcaemia =</mark> suggestive criteri	a not meeting o	<mark>criteria for major or minor</mark>	<mark>GTI = Gen</mark>	<mark>iital Tract Infection</mark>		<b>Group 3 =</b> n=153		
	hypoglycaemia hypoglycaemia hypoglycaemia hypoglycaemia hypoglycaemia hypoglycaemia hypoglycaemia hypoglycaemia	<mark>a</mark>				<mark>lypotension</mark>	Group 4 = n=	<b>Group 4 =</b> n=145		
						<mark>lypoglycaemia (severe)</mark>		2 deaths in the 5 mg dapagliflozin grou		
					HypoM =	Hypoglycaemia (mild)	2 deaths in t			
						Hypoglycaemia (other)				
	Group 1 (n ana		Group 2 (n=2		Group 3 (			Group 4 (n=194):		
	Placebo + insu			gliflozin + insulin ± OAD		agliflozin + insulin ± OAD		10 mg dapagliflozin + insulin ± OAD		
Specific events	UTI n=10, GTI	<mark>n=5</mark>	UTI n=16, GT	<mark>l n=13</mark>	UTI n=23,	GTI n=21	UTI n=20, GT	UTI n=20, GTI n=21		
	HypoT n=2		HypoT n=5		HypoT n=		HypoT n=3			
	HypoS n=2, Hy	<mark>rpoM n=99, HypoO n=11</mark>		<mark>lypoM n=118, HypoO n=19</mark>		<mark>2, HypoM n=113, HypoO n=2</mark> 4		HypoS n=3, HypoM n=99, HypoO n=23		
	Renal impairm	ent / failure n=3		ment / failure n=2		pairment / failure n=6		Renal impairment / failure n=4		
		to discontinuation n=3		ng to discontinuation n=2		ading to discontinuation n=5		ng to discontinuation n=5		
	Nasopharyngit		Nasopharyng Nasopharyng			yngitis n=35	Nasopharyng			
	Headache n=1		Headache n=		<mark>Headache</mark>		Headache n=	<u>- L</u>		
	Back pain n=11		Back pain n=:		<mark>Back pain</mark>		Back pain n=			
	Hypertension I		<b>Hypertension</b>		Hyperten:		<b>Hypertension</b>			
	Diarrhoea n=8		Diarrhoea n=		<mark>Diarrhoea</mark>		Diarrhoea n=			
		=3Peripheral oedema	<b>Constipation</b>		<b>Constipat</b>	ion n=7	Constipation n=6			
	<mark>n=15</mark>		Peripheral of			<mark>I oedema n=5</mark>		Peripheral oedema n=9		
		act Infection n=12		ract Infection n=6		sp. tract Infection n=8		tract Infection n=9		
	Arthralgia n=1	<u> </u>	Arthralgia n=	<u></u>	<b>Arthralgia</b>	n=3	Arthralgia n=	<u></u>		



# Canagliflozin

	ggarwal N, Polidori D, Zh inhibitor, as add-on to					ose Fun	ding source: Janssen	Global Services
otransporter 2	illilibitor, as add-on to	metioniiii iii subjects	with type 2 diabetes.	Diabetes care 2012, s	35(0). 1232-1238			
						or 3	T2 Inhibitor (50, 100 300 mg BD canaglifloz sus sitaglipitin + meti	in) + metformin ormin
							sus placebo + metfor	min
	he safety, tolerability ar			e 2 diabetes who hav	e inadequate glycaem	nic control on metfori	min monotherapy	
Study quality	<u> </u>	y table for further info	rmation					
Study	Multi-centre: 85 (12							
particulars	Duration of interver							
	Duration of run in: 4	weeks						
	Follow-up: 2 weeks	post-treatment						
	Design: 7-arm parall	el group RCT, double bl	lind, placebo controlle	d				
	Primary outcome: ch	hange from baseline in	HbA1c to week 12					
	Secondary outcome	s:						
	<ul> <li>Change in FPG</li> </ul>							
	<ul> <li>Change in weight</li> </ul>	ht						
	0 0	se-to-creatinine ratio						
	- Change in propo	ortion of participants w	rith HbAc <7.0% and <6	5.5%				
	- Loss of beta cell	I function measured us	ing HOMA2-%B					
	- Serum lipids							
	<ul> <li>Adverse events,</li> </ul>	, laboratory assessmen	ts, vital signs					
Participant	N: 451 analysed							
criteria		articipants with type 2 o						e (≥3 months) dose
	of ≥1500 mg/day; sta	able body weight; BMI	25 (24 for Asians) to 4	5 kg/m²; serum creatii	nine <1.5mg/dl for me	en and <1.4mg/dl for	women	
	Exclusion criteria: no	ot specifically reported						
Interventions	Intervention 1: place	ebo (pla) + metformin						
	Intervention 2: cana	gliflozin (cana) 50 mg C	DD + metformin (met)					
		gliflozin 100 mg OD + n						
		gliflozin 200 mg OD + n						
	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: sitaglintin (sita) 100 mg OD + metformin							
		gliflozin 300 mg BD + m						
		liptin (sita) 100 mg OD						
	_	ormin mean dose 1890						
		reatment screening ph						
Participant		Group 1 pla +	Group 2 cana	Group 3 cana	Group 4 cana	Group 5 cana	Group 6 cana	Group 7 sita
baseline data		met (n=65)	50 mg OD + met	100 mg OD + met	200 mg OD + met	300 mg OD + met	300 mg BD + met	100 mg OD + me
			(n=64)	(n=64)	(n=65)	(n=64)	(n=64)	(n=65)
				+ ' '	` '	, ,		( 00)
	Age (years)	53 3 SD7 8	53 3 SD8 5	51 7 SD8 0	1 52 9 SD9 6	1 52 3 51)6 9	1 55 7 50 / 1	51 7 SD8 1
	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%

	/ 2\	22.5.25.4.6			04 = 05		04.465.50	1	01.0		24.000=0	0.00000	
	BMI (kg/m²)	30.6 SD4.6	l l	SD4.6	31.7 SD		31.4 SD5.2			SD4.9	31.8 SD5.2	31.6 SD5.0	
	HbA1c (%)	7.75 SD0.83		SD0.99	7.83 SD		7.61 SD0.80	)		SD1.02	7.73 SD0.89	7.64 SD0.95	
	Diab. duration (yea	•	5.6 \$		6.1 SD4.		6.4 SD5.7		5.9 S		5.8 SD4.6	5.6 SD4.7	
	FPG (mmol/L)	9.1 SD2.1	9.4 \$		9.3 SD2.		8.9 SD2.1		8.8 S		8.7 SD1.9	8.8 SD2.3	
	SBP (mmHg)	125 SD10	127	SD11	127 SD1	.3	124 SD11		126	SD12	128 SD13	129 SD13	
Outcome (chang	ge from baseline at stu	·		1				1					
	Group 1 pla + met	Group 2 cana 5	0 mg OD	Group 3		Group 4		Group 5			Group 6 cana	Group 7 sita 100 mg	
	(n=65)	+ met (n=64)		100 mg (n=64)	OD + met	200 mg ( (n=65)	DD + met	300 mg (n=64)	OD+		00 mg BD + met n=64)	OD + met (n=65)	
ΔHbA1c (%) [SE	-0.22 SE0.08	-0.79 SE0.1		-0.76 SE	0.12	-0.70 SE	0.08	-0.92 SE	0.08	-1	0.95 SE0.08	-0.74 SE0.08	
from graph]		p<0.001 vs plac	ebo	p<0.001	vs placebo	p<0.001	vs placebo	p<0.001	vs pl	acebo p	<0.001 vs placebo	p<0.001 vs placebo	
ΔWeight (kg)	-1.1 SE0.29	-2.3 SE0.39		-2.6 SE0		-2.7 SEO.	39	-3.4 SEC			3.4 SE0.29	-0.6 SE0.39	
[SE from graph]		p<0.001 vs plac	ebo		vs placebo		vs placebo	p<0.001			<0.001 vs placebo	NS vs placebo	
ΔFPG (mmol/L)	+0.2 SE0.20	-0.9 SE0.22		-1.4 SEO	•	-1.5 SEO.	•	-1.4 SEC			1.3 SE0.20	-0.7 SE0.20	
[SE from graph]		p<0.001 vs plac	ebo	p<0.001	vs placebo	p<0.001	vs placebo	p<0.001	l vs pl	acebo p	<0.001 vs placebo	pNR	
ΔSBP (mmHg)	-1.3 SE1.5	-0.9 SE1.7, p NF		_	L.3, p NR	-2.1 SE1.	•	-4.9 SE1			3.6 SE1.4, p NR	-0.8 SE1.4, p NR	
Adverse events				YO		1	, i	ı			/	· · · · · · · · · · · · · · · · · · ·	
Safety assessme	ent: adverse event rep	orts (Medical Dictiona	ary for Reg	ulatory Act	ivities), vital si	gns, physic	cal examinatio	ns, labora	tory a	assessments	, self-administered va	ginal swabs	
		ia (HypoM) = symptor	, ,		eral events –	<u> </u>		•			e or more adverse ev	<u> </u>	
	capillary glucose <3.5				UTI = Urinary Tract Infection					<b>Group 1 =</b> n=26			
		n <b>ia</b> (HypoS) = sympton	natic eniso						Group 2 = n=32				
		istance with following		1	Hypo = Hypoglycaemia HypoT = AEs suggestive of hypotension					Group 3 = n=30 Group 4 = n=26 Group 5 = n=26			
	capillary glucose <3.0	_	, recovery,										
	. , ,	<b>a</b> (HypoO) = symptom	s hut	,,									
	without measuremen		15, 540							Group 6 = n=36 Group 7 = n=23			
	Without incusuremen	nt comming											
		<b>Group 1</b> pla (n=65)	Group 2	cana	Group 3 car	าว	Group 4 cana	6	iroun	<b>5</b> cana	Group 6 cana	Group 7 sita	
		Group I pia (II-05)	50 mg O		100 mg OD		200 mg OD (n			g OD (n=64)	300 mg BD (n=64)	100 mg OD (n=65)	
Specific	UTI	n=4	n=3	J (11-04)	n=2		n=6		=2	5 00 (11-04)	n=3	n=1	
Events	GTI	n=1	n=5		n=4		n=2	4	-2 =2		n=4	n=1	
LVEIILS	Symptomatic Hypo	n=1	n=0		n=1		n=4		=0		n=2	n=3	
	НуороТ	n=1	n=0		n=4		n=3		-0 =1		n=1	n=1	
	AEs leading to	n=2	n=0 n=1		n=3		n=1		=2		n=2	n=0	
	discontinuation	11-2	11-1		11-5		11-1	"	-2		11=2	11-0	
		m_2	n_1				n-2		_2		n-1	n-1	
	Headache	n=2	n=1		n=5		n=2		=3 -2		n=1	n=1	
	Nausea	n=0	n=3		n=1		n=1		=3		n=5	n=1	
	Nasopharyngitis	n=2	n=5		n=0		n=0		=1		n=1	n=3	
	Diarrhoea	n=2	n=1		n=1		n=0		=2		n=3	n=2	
	Pollakiuria	n=1	n=2		n=3		n=1		=2		n=0	n=2	
	Vulvovaginal	n=0	n=4		n=2		n=4	n	=1		n=3	n=1	
	mycotic infect.				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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# 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
3 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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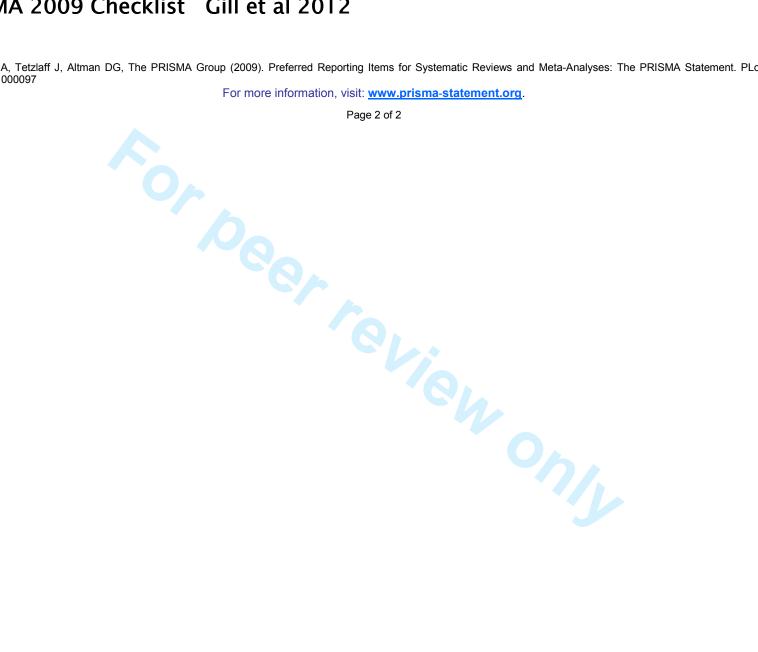
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4 5	Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis.	N/A
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7		Page 1 of 2				
8 9 Section/topic	#	Checklist item	Reported on page #			
11 Risk of bias across studies 12	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A			
13 14 Additional analyses 15	16	scribe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating ich were pre-specified.				
16 RESULTS						
18 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			
20 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			
23 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			
27 Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a			
<sup>28</sup> Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6			
30 Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a			
32 DISCUSSION	1					
33 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			
36 Limitations 37	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			
38 Conclusions 39	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12			
40 FUNDING						
42 Funding 43	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



# 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	Fair points, but we can only report what research
discussing the SGTL2	there is.
receptor inhibitors used as combination therapy	And it is not correct that only one trial had an
for treatment of type	active comparator – there were two active
2 diabetes. While this is an important topic as we	comparators, glipizide in Nauck 2011 and
need to know what	sitagliptin in Rosenstock 2010.
is the best 2nd and 3rd line agent for type 2	Stagnpen in Noscristock 2010.
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.	
1) The introduction needs to address why this	Section added at end of Introduction with
topic needed a	similar message to referee's comments, and
systematic review. i.e. Few people know about	mentioning safety.
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	
critically stitle you do also	

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	Figures for HbA1c changes added to Abstract.  No change to "good quality" – it's a standard expression in systematic reviews.
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.	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.  10) Would start methods before study participants and all the	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.  Methods now starts as suggested.  Subheadings retained
following information should be put without bullets under one of the three headings mentioned above.	
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

moved to Adverse events section
point. Sentence deleted.
change. There could be ceiling effects in erse events too
text revised and we have added the figures in Nauck, the largest study and calculated centages and CIs.
e bit removed and paragraph on FDA review ed.

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
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%	
337 413 517 676	
-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	Figures were as calculated in original studies.
calculation perfomed and which statistical package was used to get to this value? This value should be obtained using meta-analysis.	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 dosagebetween 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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