

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

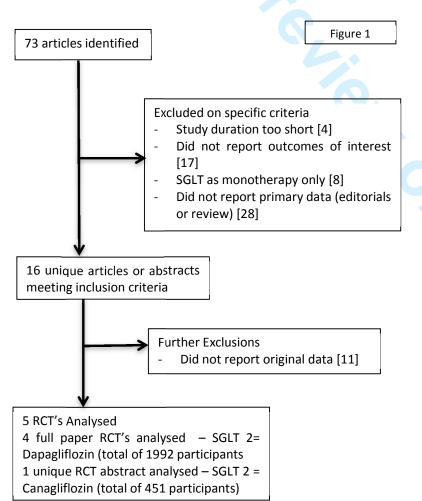
Study Selection: two reviewers using the defined criteria above selected studies independently. Any resulting discrepancies were resolved by discussion, with minimal third party mediation required.

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 32.7kg/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-

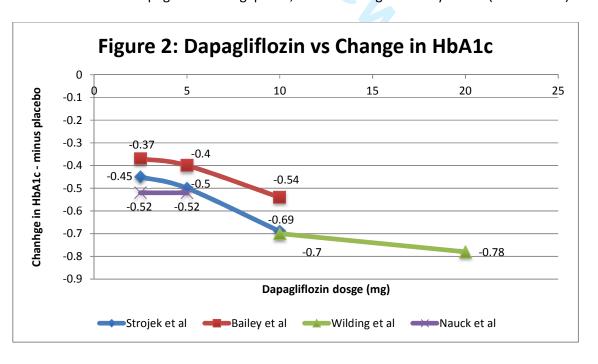
		Blinding and double dummy)	record carried forwards				0.35% difference detectable	Zeneca and Bristol- Myers- Squibb
Rosenstock 2010	Not reported	Yes (double blinding	Not reported	Not reported	Unclear	Yes	No comment on sample size calculation	Johnson and Johnson
Strojek 2011	Yes	Yes (Double Blinding and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

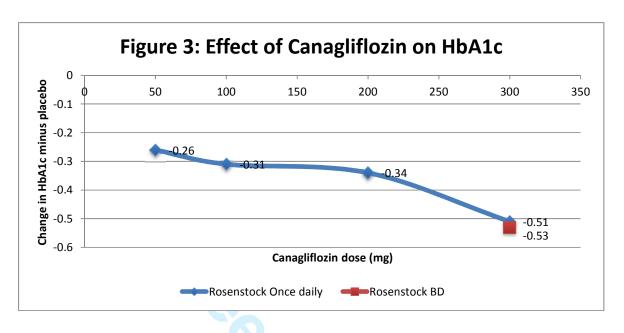
Results

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)

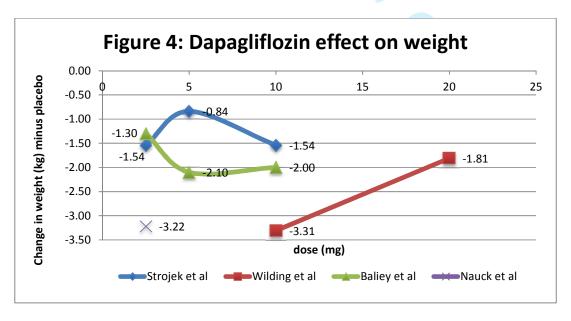
The SGLT2 inhibitors were shown, as demonstrated on Fig 2., to reduce HbA1c by between -0.52 and -0.78% when adjusted for changes on placebo. There was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by 0.52% (Nauck 2011).





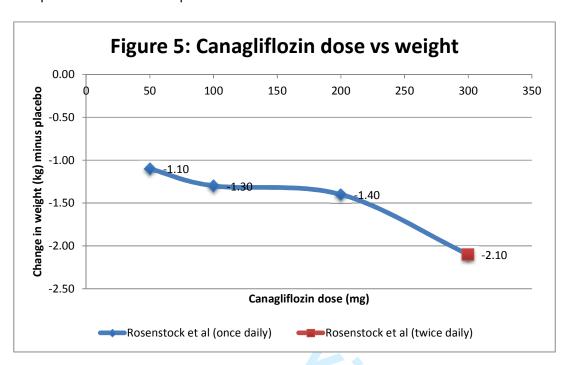
Body weight

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 Strokiek (2011).

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

Adverse events

Urinary and genital tract infection

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

Hypoglycaemia

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

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

Nauck (2011), indicates that compared to glipizide, dapagliflozin produced a significant reduction in all types of hypoglycaemic events, with an incidence of 3.4%, compared to 39.7%, being 14 vs 150 events.

Other Adverse Events

Across all studies, two deaths were reported in dapagliflozin groups, both by Strojek (2011), attributed to cardiopulmonary arrest, and pulmonary embolism after ischaemic stroke respectively. Neither event was considered to be the result of the study medication.

Three deaths were also reported by Nauck (2011) in the glipizide placebo group, none in the SGLT2 group.

Discussion

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

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

- iii) Lowering systolic blood pressure
- iv) Decreasing FPG levels

Given the mechanism of action of the SGLT2 receptor inhibitors, hypoglycaemia would be expected to be less, and has been an important study outcome (8). Nauck (2011) in one of the largest studies (801 participants), found a significantly higher incidence of hypoglycaemia in the sulphonylurea group, than with dapagliflozin. Hypoglycaemia in patients treated with SGLT2 receptor inhibitors was seen most when used in combination with insulin.

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

Implications for future practice

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

- Metformin
- The sulphonylureas
- Pioglitazone
- Acarbose
- The meglitinide analogues, nateglinide and repaglinide
- The GLP-1 analogues
- The DPP-4 inhibitors
- The SGLT inhibitors
- Insulins

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

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

The fear of hypoglycaemia can have a significant impact on the patient's quality of life. The studies in this review recruited patients who were poorly controlled on present medications. Future trials might examine the role of the SGLT2 inhibitors in reducing the frequency of hypoglycaemic episodes in patients with good control but at the cost of

hypoglycaemia. There is also the potential for their evaluation for use in poorly controlled type I diabetes.

Limitations of studies reviewed

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

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

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

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

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

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

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

Conclusion

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

Competing interests of authors

None

Funding source - internal department

References

1. Diabetes UK,

Diabetes in the UK 2010: Key statistics on Diabetes

http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf (Accessed October 1st 2011)

- 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

6. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications.

Report of a WHO Consultation, WHO/NCD/NCS/99.2 (2000) http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf (Accessed Sept 20th 2011)

7. Higgins J. and Green S.

Cochrane Handbook for Systematic Reviews of Interventions (2008)

The Cochrane Collaboration http://www.cochrane.org/training/cochrane-handbook (Accessed Sept 1st 2011)

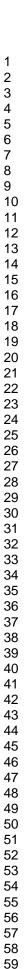
8. Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L, et al Dapagliflozin a novel SGLT2 inhibitor induces dose-dependent glucosuria in healthy subjects.

Clin. Pharmacol Ther. 2009; 85:520-6

9. Musso G, Gambino R, Cassader M, Pagano G.

A novel approach to control hyperglycaemia in type 2 diabetes: Sodium glucose cotransport (SGLT) inhibitors. Systematic review and meta-analysis of randomised trials

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



Appendix

	SJL, Pieters A, Bastien A, List JF. Sliflozin in patients with type 2 diabetes who Ned trial	o have inadequate glycaemic control with	metformin: a randomised, double-blind,	Funding source: Astra-Zeneca and Bristol-Myers-Squibb					
•	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	entrol 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	02 week long-term study							
	Design: 4-arm RCT, double blind, placebo	controlled							
	Primary outcome: Change from baseline in	h 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								
	 No. with baseline HbA1c of 9% o 	r more. 222 Change from baseline in	bodyweight, and decreases in bodyweight o	of 5% or more.					
Participant	N: 534 analysed								
Criteria	Inclusion criteria: participants aged betwe metformin>1500mg	en 18 years and 77; Type 2 diabetes, BMI <	45kg/m2, HbA1c 7-10.0%; fasting C-peptide	e >0.34ng/ml, taking stable dose					
			or 124 μmol/L or more for women (consist						
				imes the upper limit of normal; symptoms of ent); and systolic blood pressure 180 mm Hg					
	or more or diastolic blood pressure 110 mi	m Hg or more. Any significant other system	nic disease						
	Load in poriod. 2 weeks single blind to a	sees compliance with placebo maticate as	ndomised successful completion. Metformi	does stabilized to >1500mg					
Quality	Study Quality: medium – See Quality table		idomised successful completion. Metformil	I nose staniiisen to >1300iiik					
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,					
	Age: 53.7 SD 10.3 years	Age: 55.0 SD 9.3 years	Age: 54.3 SD 9.4 years	Age: 52.7 SD 9.9 years					
	Sex: 55% Male	Sex: 51% Male	Sex: 50% Male	Sex: 57% male					
	BMI (KG/M ²): 31.8 SD 5.3	BMI (KG/M²): 31.6 SD 4.8	BMI (KG/M²): 31.4 SD 5.0	BMI (KG/M ²): 31.2 SD 5.1					
	HbA1c (%): 8.11% SD 0.96	HbA1c (%): 8.96% SD 2.39	HbA1c (%): 8.17% SD 1.0	HbA1c (%): 7.92% SD 0.82					
	Duration of Diabetes: 5.8 SD 5.1	Duration of Diabetes: 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): 8.96 SD 6.2 Systolic BP: 126.6 SD 14.5		FPG (mmol/l): 9.39 SD 2.7 Systolic BP: 126.9 SD 14.3		FPG (mmol/l): 8.66 SD 2.15 Systolic BP: 126.0 SD 15.9		
Outcome (chan	l lge from baseline a	at study end)			<u> </u>				
•	Group 1 (n analy Placebo OD + m	ysed=134):				Group 3 (n= 133): 5mg dapagliflozin OD, metformin		Group 4 (n= 132): 10mg dapagliflozin OD,	
	Mean	Mean Confidence (95%)		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	
·					7.42	0.94	7.13	0.94	
Adverse		1.18 caemia = symptomatic episo			>5%	– where frequency is	At least one Group 1 = n=	or more adverse event	
Adverse	Minor hypoglyo		ode, capillary glucos	se <3.5mmol/l)	General events	- where frequency is ract Infection act Infection ension	At least one	or more adverse event 88 89 95	
HbA1c Adverse Events	Minor hypoglyo	caemia = symptomatic episo caemia = symptomatic episo ery, capillary glucose <3.0mi	ode, capillary glucos	se <3.5mmol/l) nal assistance with	General events >5% UTI = Urinary Tr GTI = Genital Tr HypoT = Hypote	- where frequency is act Infection act Infection ension lycaemia	At least one Group 1 = n= Group 2 = n= Group 3 = n=	or more adverse event :88 :89 :95	
Adverse	Minor hypoglyc Major hypoglyc following recove	caemia = symptomatic episo caemia = symptomatic episo ery, capillary glucose <3.0mi	ode, capillary glucos ode, needing extern mol/l) Group 2 (n= 13	se <3.5mmol/l) nal assistance with	General events >5% UTI = Urinary Tr GTI = Genital Tr HypoT = Hypote HypoG = Hypog Group 3 (n= 133)	- where frequency is act Infection act Infection ension lycaemia	At least one Group 1 = n= Group 2 = n= Group 3 = n= Group 4 = n=	or more adverse event -88 -89 -95 -98	
Adverse Events Specific	Minor hypoglyc Major hypoglyc following recove Group 1 (n anal Placebo OD + n UTI: n= 11, GTI	caemia = symptomatic episo caemia = symptomatic episo ery, capillary glucose <3.0mi lysed=134): metformin, n = 7,	de, capillary glucos de, needing extern mol/l) Group 2 (n= 13: 2.5mg dapaglifl	se <3.5mmol/l) hal assistance with 5): ozin OD, metformin = 11	General events >5% UTI = Urinary Tr GTI = Genital Tr HypoT = Hypote HypoG = Hypog Group 3 (n= 13: 5mg dapaglifloz UTI: n= 10, GTI i	- where frequency is ract Infection act Infection ension lycaemia 3): in OD, metformin	At least one Group 1 = n= Group 2 = n= Group 3 = n= Group 4 = n= 10mg dapagl	or more adverse event	
Adverse Events Specific	Minor hypoglyc Major hypoglyc following recove Group 1 (n anal Placebo OD + n UTI: n= 11, GTI (HypoT n=1, Hyp	caemia = symptomatic episo caemia = symptomatic episo ery, capillary glucose <3.0mi lysed=134): metformin, n = 7, poG n=4,	Group 2 (n= 13: 2.5mg dapaglifl UTI: n= 6 GTI n HypoT n=0, Hyp	se <3.5mmol/l) hal assistance with 5): ozin OD, metformin = 11	General events >5% UTI = Urinary Tr GTI = Genital Tr HypoT = Hypote HypoG = Hypog Group 3 (n= 13: 5mg dapaglifloz UTI: n= 10, GTI I HypoT n=2, Hyp	- where frequency is ract Infection act Infection ension lycaemia 3): in OD, metformin	At least one Group 1 = n= Group 2 = n= Group 3 = n= Group 4 = n= Group 4 (n= 10mg dapagl UTI: n= 16, G HypoT n=0, H	or more adverse event	
Adverse Events	Minor hypoglyc Major hypoglyc following recove Group 1 (n anal Placebo OD + n UTI: n= 11, GTI (HypoT n=1, Hyp Diarrhoea n= 7	caemia = symptomatic episo caemia = symptomatic episo ery, capillary glucose <3.0mi lysed=134): metformin, n = 7, poG n=4,	Group 2 (n= 13: 2.5mg dapaglifl UTI: n= 6 GTI n HypoT n=0, Hyp Diarrhoea n= 3	se <3.5mmol/l) hal assistance with 5): ozin OD, metformin = 11	General events >5% UTI = Urinary Tr GTI = Genital Tr HypoT = Hypote HypoG = Hypog Group 3 (n= 13: 5mg dapaglifloz UTI: n= 10, GTI i	- where frequency is ract Infection act Infection ension lycaemia 3): in OD, metformin	At least one Group 1 = n= Group 2 = n= Group 3 = n= Group 4 (n= 10mg dapagl UTI: n= 16, G HypoT n=0, H Diarrhoea n=	or more adverse event	
Adverse Events Specific	Minor hypoglyc Major hypoglyc following recove Group 1 (n anal Placebo OD + n UTI: n= 11, GTI (HypoT n=1, Hyp	caemia = symptomatic episo caemia = symptomatic episo ery, capillary glucose <3.0mi lysed=134): metformin, n = 7, poG n=4,	Group 2 (n= 13: 2.5mg dapaglifl UTI: n= 6 GTI n HypoT n=0, Hyp	se <3.5mmol/l) hal assistance with 5): ozin OD, metformin = 11 poG n=3	General events >5% UTI = Urinary Tr GTI = Genital Tr HypoT = Hypote HypoG = Hypog Group 3 (n= 13: 5mg dapaglifloz UTI: n= 10, GTI II HypoT n=2, Hyp Diarrhoea n= 5	- where frequency is act Infection act Infection ension lycaemia 3): in OD, metformin n = 18 acg n=5,	At least one Group 1 = n= Group 2 = n= Group 3 = n= Group 4 = n= Group 4 (n= 10mg dapagl UTI: n= 16, G HypoT n=0, H	or more adverse event	
Adverse Events Specific	Minor hypoglyc Major hypoglyc following recove Group 1 (n anal Placebo OD + n UTI: n= 11, GTI HypoT n=1, Hyp Diarrhoea n= 7 Back pain n= 7	caemia = symptomatic episo caemia = symptomatic episo ery, capillary glucose <3.0mi lysed=134): metformin, n = 7, poG n=4,	Group 2 (n= 13: 2.5mg dapaglifl UTI: n= 6 GTI n HypoT n=0, Hyp Diarrhoea n= 3 Back pain n= 5	se <3.5mmol/l) hal assistance with 5): ozin OD, metformin = 11 poG n=3	General events >5% UTI = Urinary Tr GTI = Genital Tr HypoT = Hypote HypoG = Hypog Group 3 (n= 13: 5mg dapaglifloz UTI: n= 10, GTI HypoT n=2, Hyp Diarrhoea n= 5 Back pain n= 3	- where frequency is act Infection act Infection ension lycaemia 3): in OD, metformin n = 18 acg n=5,	At least one Group 1 = n= Group 2 = n= Group 3 = n= Group 4 (n= 10mg dapagl UTI: n= 16, G HypoT n=0, H Diarrhoea n= Back pain n=	or more adverse event	
Adverse	Minor hypoglyc Major hypoglyc following recove Group 1 (n anal Placebo OD + n UTI: n= 11, GTI HypoT n=1, Hyp Diarrhoea n= 7 Back pain n= 7 Nasopharyngitis	caemia = symptomatic episo caemia = symptomatic episo ery, capillary glucose <3.0mi lysed=134): metformin, n = 7, poG n=4,	Group 2 (n= 13: 2.5mg dapaglifl UTI: n= 6 GTI n HypoT n=0, Hyp Diarrhoea n= 3 Back pain n= 5 Nasopharyngitis	se <3.5mmol/l) hal assistance with 5): ozin OD, metformin = 11 poG n=3 s n= 12	General events >5% UTI = Urinary Tr GTI = Genital Tr HypoT = Hypote HypoG = Hypog Group 3 (n= 13: 5mg dapaglifloz UTI: n= 10, GTI HypoT n=2, Hyp Diarrhoea n= 5 Back pain n= 3 Nasopharyngitis	- where frequency is act Infection act Infection ension lycaemia 3): in OD, metformin n = 18 acg n=5,	At least one Group 1 = n= Group 2 = n= Group 3 = n= Group 4 (n= 10mg dapagl UTI: n= 16, G HypoT n=0, H Diarrhoea n= Back pain n= Nasopharyng	or more adverse event	
Adverse Events Specific	Minor hypoglyc Major hypoglyc following recove Group 1 (n anal Placebo OD + n UTI: n= 11, GTI HypoT n=1, Hyp Diarrhoea n= 7 Back pain n= 7 Nasopharyngitis Cough n= 7	caemia = symptomatic episo caemia = symptomatic episo ery, capillary glucose <3.0mi lysed=134): metformin, n = 7, poG n=4,	Group 2 (n= 13: 2.5mg dapaglifl UTI: n= 6 GTI n HypoT n=0, Hyp Diarrhoea n= 3 Back pain n= 5 Nasopharyngitis Cough n= 4	se <3.5mmol/l) hal assistance with 5): ozin OD, metformin = 11 poG n=3 s n= 12	General events >5% UTI = Urinary Tr GTI = Genital Tr HypoT = Hypote HypoG = Hypog Group 3 (n= 13: 5mg dapaglifloz UTI: n= 10, GTI HypoT n=2, Hyp Diarrhoea n= 5 Back pain n= 3 Nasopharyngitis Cough n= 4	- where frequency is act Infection act Infection ension lycaemia 3): in OD, metformin n = 18 oG n=5,	At least one Group 1 = n= Group 2 = n= Group 3 = n= Group 4 (n= 10mg dapagl UTI: n= 16, G HypoT n=0, H Diarrhoea n= Back pain n= Nasopharyng Cough n= 1	or more adverse event	
Adverse Events Specific	Minor hypoglyc Major hypoglyc following recove Group 1 (n anal Placebo OD + n UTI: n= 11, GTI HypoT n=1, Hyp Diarrhoea n= 7 Back pain n= 7 Nasopharyngitis Cough n= 7 Influenza n= 10 Hypertension ns	caemia = symptomatic episo caemia = symptomatic episo cery, capillary glucose <3.0mi lysed=134): metformin, n = 7, poG n=4, s n= 11 = 6 act Infection n= 10	Group 2 (n= 13: 2.5mg dapaglifl UTI: n= 6 GTI n HypoT n=0, Hyp Diarrhoea n= 3 Back pain n= 5 Nasopharyngitis Cough n= 4 Influenza n= 13 Hypertension n	se <3.5mmol/l) hal assistance with 5): ozin OD, metformin = 11 poG n=3 s n= 12	General events >5% UTI = Urinary Tr GTI = Genital Tr HypoT = Hypote HypoG = Hypog Group 3 (n= 13: 5mg dapaglifloz UTI: n= 10, GTI HypoT n=2, Hyp Diarrhoea n= 5 Back pain n= 3 Nasopharyngitis Cough n= 4 Influenza n= 13 Hypertension ns	- where frequency is act Infection act Infection ension lycaemia 3): in OD, metformin n = 18 oG n=5,	At least one Group 1 = n= Group 2 = n= Group 3 = n= Group 4 (n= 10mg dapagl UTI: n= 16, G HypoT n=0, H Diarrhoea n= Back pain n= Nasopharyng Cough n= 1 Influenza n= Hypertension	or more adverse event -88 -89 -95 -98 132): iflozin OD, TI n =12, HypoG n=5 -10 -10 -10 -10 -10 -10 -17 -17 -18 -18 -18 -18 -18 -18 -18 -18 -18 -18	

Dapagliflozin Vs Gli	o S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al pizide as Add-on Therapy in Patients with Type 2 diabetes v	vho have inadequate glycaemic control with Metformin	Funding source: Astra-Zeneca and Bristol-Myers-Squibb					
Diabetes care 2011	34:[2015-2022]		SGLT2 Inhibitor + metformin vs metformin + glipizide					
Aim: Compare effic	acy, safety and tolerability of dapagliflozin with glipizide, in p	atients 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-ter	rm study						
	Design: 2-arm parallel group, RCT.							
	Primary outcome: Absolute change from baseline in HbA1	c 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/							
		albumin: creatinine ratio >203.4 mg/mmol; AST and/or ALT and/onen and ≤10 g/dL for women; abnormal TSH; systolic blood pressu						
Interventions	Intervention 1: 2.5mg dapagliflozin + metformin							
	Intervention 2: 5mg glipizide + metformin							
	Lead in period: 2 weeks, single blind placebo lead in prior							
	All groups: Patients randomly assigned to double blind the	erapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pa	tients maintained metformin					
•	All groups: Patients randomly assigned to double blind the Study Quality: medium – See Quality table for further info	erapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All parmation						
Participant	All groups: Patients randomly assigned to double blind the Study Quality: medium – See Quality table for further info Group 1 (start n= 406, analysed n=400):	erapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All parmation Group 2 (start n= 408, analysed n= 401)						
Participant	All groups: Patients randomly assigned to double blind the Study Quality: medium – See Quality table for further info Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin	erapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All parmation Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin						
Participant	All groups: Patients randomly assigned to double blind the Study Quality: medium – See Quality table for further info Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin Age: 58 SD 9 years	erapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All parmation Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin Age: 59 SD 10 years						
Participant	All groups: Patients randomly assigned to double blind the Study Quality: medium – See Quality table for further info Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin Age: 58 SD 9 years Sex: 55.3% Male	erapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All parmation Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin Age: 59 SD 10 years Sex: 54.9§% Male						
Quality Participant baseline data	All groups: Patients randomly assigned to double blind the Study Quality: medium – See Quality table for further info 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	erapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All parmation Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin Age: 59 SD 10 years 5ex: 54.9§% Male BMI (KG/M²): 31.2 SD 5.1						
Participant	All groups: Patients randomly assigned to double blind the Study Quality: medium – See Quality table for further info Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin Age: 58 SD 9 years Sex: 55.3% Male	erapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All parmation Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin Age: 59 SD 10 years Sex: 54.9§% Male						
Participant	All groups: Patients randomly assigned to double blind the Study Quality: medium – See Quality table for further info 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	erapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All parmation Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin Age: 59 SD 10 years 5ex: 54.9§% Male BMI (KG/M²): 31.2 SD 5.1						
Participant	All groups: Patients randomly assigned to double blind the Study Quality: medium – See Quality table for further info 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%%	rmation 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/l): 9.1 SD 2.3			
Outcome (change	from baseline at study end)					
	Group 1 (start n= 406, analysed n= 2.5mg dapagliflozin + metformin	400):	Group 2 (start n= 408, analysed n= 401): 5mg glipizide + metformin			
	Mean	Confidence (95%)	Mean	Confidence (95%)		
Δ HbA1c (%)	-0.52	-0.60 to -0.44	-0.52	-0.60 to -0.44		
Δ Weight (kg)	-3.22 -3.56 to -2.87		+1.44	+1.44		
Δ FPG (mmol/L)	-1.24	-1.42 to -1.07	-1.04	-1.22 to -0.98		
	Mean	SD	Mean	SD		
Δ SBP (mmHg)	-4.3	-	-+0.8	-		
HbA1c	-	-	-	-		
		A				
Adverse Events	Minor hypoglycaemia (HypoM) = symptomatic episode, capillary glucose <3.5mmol/l) Severe hypoglycaemia (HypoS) = symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/l) Other hypoglycaemia (HypoO) = symptoms, but without measurement confirming		General events – where frequency is ≥3% UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia other	At least one or more adverse event Group 1 = n=318 Group 2 = n=318 No deaths in Dapagliflozin group 3 deaths in Glipizide group		
	Group 1		Group 2			
Specific Events	UTI: n=44, GTI n = 50, HypoM n= 0 HypoS n= 7 HypoO, n=7 Events Leading to Discontinuation Diarrhoea n= 19 Nausea n= 14 Vulvovaginal mycotic infection n= Back pain n= 19 Nasopharyngitis n= 43 Cough n= 15 Influenza n= 30 Pain in extremity n= 11 Upper resp. Tract Infection n= 24 Headach n= 21		UTI: n=26, GTI n = 11, HypoM n= 3 HypoS n= 147 HypoO, n=40 Events Leading to Discontinuation, n=6 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			
Safety	Hypertension n= 30 Assessed via adverse events from	the Medical Dictionary or Regulatory Activiti	Hypertension n= 35 es (MedDRA v12.1) via patient questionnaire	and active questioning during visits		
Assessment	7.55555Cd vid ddver5c events from	the medical Dictionary of Regulatory Activity	to (meables viz.i) via patient questionnane	and delive 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
•	type 2 diabetes on background metformin 2010 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 volin 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 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	HA1c (%): 7.7% Duration of Dia FPG (mmol/l): 9 Systolic BP: -	Sex: - BMI (KG/M²): 31.5 HA1c (%): 7.7% Duration of Diabetes: - FPG (mmol/l): 9.0									
Outcome (chan	Group 1 placeb		Group 2 canag	liflozin 50mg +	Group 3 canagli	iflozin 100mg + metformin	Group 4 can	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 canagli	iflozin 300mg + metformin	Group 6 canag metformin	liflozin 300mg BD +	Group 7 sitaglip	otin + metformin					
	Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)					
Δ HbA1c (%)	-0.71	-	-0.73	-	-0.56	-					
Δ Weight (kg)	-2.3	-	-2.3	-	+0.4	-					
Δ FPG (mmol/L)	-1.8	-	-1.7	-	-1.0	-					
	Mean	SD	Mean	SD	Mean	SD					
Δ SBP (mmHg)	-	-	-	-	-	701					
HbA1c	6.8	0.82	6.8	0.72	6.9	0.92]				
Adverse Events	At least one or	more adverse event balance	d across all arms	save for:							
Specific	Genital tract in	fections:	UTI		Hypoglycaemic	a (not defined in					
Events	3-8% canagliflo	zin arms	3-9% canaglifl	ozin arms	abstract)						
	2% placebo 2% sitagliptin		6% placebo 2% sitagliptin		0-6% canagliflo 2% placebo 5% sitagliptin	zin arms					

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

	KH, Hruba V, Elze M, Langkilde AM, Parikh S.	Funding source: Astra-Zeneca and
•	gliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-controlled trial.	Bristol-Myers-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 with inadequately contri Iphonylurea 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 24 selline if BMI ≥27kg/m²	
Participant Criteria	 FPG from baseline after 24weeks N: 592 analyzed 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 gluco 	

	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 creat 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 DE 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									
		5 mg/day dapagiiiloziii pius 2 10 mg/day dapagliflozin plus								
		1 week for inclusion/exclusion			glimepiride					
	titration allowed	ngliflozin double-blind, glime d; in case of inadequate glyca tyle counseling and patients	emic control, pa	atients could receive oper	n-label rescue the	rapy of metformin, pioglit	azone or rosigli	tazone; all patients receive		
Quality		Medium – See Quality table f					•	•		
Participant	Group 1 (n= 146	5)	Group 2 (n= 1	154)	Group 3 (n= 14!	5)	Group 4 (n=	151)		
baseline data	Placebo + glime	piride	2.5mg dapagl	iflozin + glimepiride	5mg dapagliflozin + glimepiride		10mg dapagl	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			
	Sex: 49% male BMI (kg/m²)		Sex: 50% male BMI (kg/m²)		Sex: 50% male BMI (kg/m²)		Sex: 43.7% male BMI (kg/m²)			
	BMI (kg/m ⁻) ≥ 25 kg/m ² : 86.2%		≥ 25 kg/m ² : 84.4%		≥ 25 kg/m ² : 78%		≥ 25 kg/m ² : 79.4%			
	\geq 30 kg/m ² : 45.5%		≥ 30 kg/m ² : 48%		≥ 30 kg/m² : 50%		\geq 30 kg/m ² : 45.%			
	HbA1c (%): 8.15	SD 0.74	HbA1c (%): 8.11, SD 0.75		HbA1c (%): 8.12 SD 0.78		HbA1c (%): 8.07 SD 0.79			
	Duration of diak	petes (years): 7.4SD 5.7	Duration of diabetes (years): 7.7 SD		Duration of diabetes (years): 7.4 SD 5.7		Duration of diabetes (years): 7.2 SD 5.5			
	FPG (mmol/L): 9	9.58 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		FPG (mmol/L): 9.56, SD 2.13 Systolic BP (mmHg): 134.6		Systolic BP (mmHg): 130.9		Systolic BP (mmHg): 133.8 SD 15			
Outcome (chan	ge from baseline a	t study end)	Systolic Br (Illing). 134.0							
	Group 1 (n= 146		Group 2 (n= 1	154)	Group 3 (n= 145)		Group 4 (n= 151)			
	Placebo + glime	piride	2.5mg dapagl	iflozin + glimepiride	5mg dapaglifloz	zin + glimepiride	10mg dapagl	iflozin + 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		
	-0.72 -		-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	-1.20	-	-4.7	-6.1 to -0.9	-4.0	-5.5 to -0.2	-3.8	-6.4 to -1.2	
SBP from									
placebo									
(mmHg)									
HbA1c	-	-	-	-	-	-	-	-	
	T						T		
Adverse Events	General events – w		:3% in any group		,, 0,	defined as blood sugar		or more adverse even	
	UTI = Urinary Tract				<70mg/dl)		Group 1 = n=		
	GTI = Genital Tract I						Group 2 = n=		
	Hypo = Hypoglycaer	mia					Group 3 = n=		
							Group 4 = n=	76	
							1 death in Dapagliflozin 2.5mg		
							1 death in Dapagliflozin 10mg		
	Group 1 (n= 146)		Group 2 (n= 154) 2.5mg dapagliflozin + glimepiride		Group 3 (n= 145) 5mg dapagliflozin + glimepiride		Group 4 (n= 151)		
	Placebo + glimepirio	de					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 Arthralgia n= 0		Back pain n= 7 Nasopharyngitis n= 5		
	Nasopharyngitis n=	4	Nasopharyngitis	n= 3					
	Arthralgia n= 4		Arthralgia n= 6	Arthralgia n= 6		Upper resp. Tract Infection n= 6		Arthralgia n= 1	
	Upper resp. Tract In	fection n= 4	Upper resp. Trac	t Infection n= 5	Hypertension n=	= 2	Upper resp. Tract Infection n= 4		
	Hypertension n= 6		Hypertension n=				Hypertension		
Safety	Assessed via advers	e events from the I	Medical Dictionary or Re	gulatory Activties (N	MedDRA v12.1) via pa	atient questionnaire and	active questioni	ng during visits	
Assessment									

A Study of Dapaglif	<i>.</i> . • • •	oses of Insulin Plus Insulin Sensitizers. Applicability of a n	Funding source: Astra-Zeneca and Bristol-Myers-Squibb				
independent treatn Diabetes care 2009			SGLT2 Inhibitor + patients own oral antidiabetic drugs (OAD) Vs insulin + OAD				
Aim: Determine if D	Dapagliflozin, lowers HBA1c in Type 2 diabetes in patients	with type 2 diabetes poorly controlled with high insulin of	loses plus oral antidiabetic agents				
Study Particulars	Multi Centre: 26 sites (USA and Canada) Duration of intervention: 52 weeks Duration of run in: 2 weeks						
	Followup: on completion of 52 weeks, a 156 week long-term study Design: 2-arm parallel group, RCT						
	Primary outcome: Change from baseline in HbA1c at week 12						
	Secondary outcomes: - Change from baseline FPG - Change in total daily requirement of insulin - Percentage of patients with change in HbA1c - Percentage of end patients with final HbA1c						
Participant Criteria	icipant N: 65 analysed						
	Exclusion criteria: Type 1 diabetes, AST and/or ALT >2. uncontrolled diabetes including a history of severe hyp	5 times the upper limits of normal, creatine kinase ≥3 timoglycemia. Any significant other disease	nes the upper limits 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						
	dose adjustments to OADs; insulin could be down-titra	ted in patients at risk of hypoglycaemia	r local guidelines); following lead in period there were no				
0 I''	Lead in period: 10-21 day to establish reduced insulin dose						
Quality	Study Quality: Medium – See Quality table for further		0 0/ 00				
Participant	Group 1 (n analysed=19):	Group 2 (n= 23):	Group 3 (n= 23):				
baseline data	Placebo, OADs + insulin,	10mg dapagliflozin, OADs + insulin,	20mg dapagliflozin OD, OADs + insulin,				

	Age (years): 58.4 SD 6.5 Sex: 69.6% male			Age (years): 55.7 SD 9.2 Sex: 54.2% male		Age (years): 56.1 SD 10.6 Sex: 54.2% male	
	BMI (kg/m²): 34.8 SD 4		BMI (kg/m²): 35.5 S			BMI (kg/m ²): 36.2 SD 4.6	
	HbA1c (%): 8.40% SD (HbA1c (%): 8.4% SE		HbA1c (%):8.5% SI		
	Duration of diabetes (•		es (years): 11.8 SD 5.8		tes (years): 11.3 SD 5.6	
	FPG (mmol/L): 9.22 SE		FPG (mmol/L): 8.67			FPG (mmol/L): 8.98 SD 3.06	
	Systolic BP (mmHg): n		Systolic BP (mmHg): n/a		Systolic BP (mmHg	Systolic BP (mmHg): n/a	
Outcome (change	from baseline at study er		1				
	Group 1 (n analysed=19):		Group 2 (n= 23):		Group 3 (n= 23):		
	Placebo, OADs + insul		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 mo	At least one or more adverse event	
	capillary glucose <3.5n	nmol/L)	UTI = Urinary Tract Infection		Group 1 = n=15	Group 1 = n=15	
	Major hypoglycaemia	= symptomatic episode,	GTI = Genital Tract Infection		Group 2 = n=18		
	needing external assist	tance with following recovery,	HypoT = Hypotension		Group 3 = n=16		
	capillary glucose <3.0n	nmol/l)	HypoG = Hypoglycaemia		One patient in each group discontinued due to		
					adverse effects	adverse effects	
Specific Events	Group 1 (n analysed=1	19):	Group 2 (n= 23):		Group 3 (n= 23):	* · · · · · · · · · · · · · · · ·	
	Placebo, OADs + insul	in,	10mg dapagliflozin, OADs + insulin,		20mg dapagliflozir	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 r	n=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	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 Infe	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 n= 1	
					Upper resp. Tract I	Infection n= 1	

Safety Assessment





47

PRISMA 2009 Checklist Gill et al 2012

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



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Synthesis of results 14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
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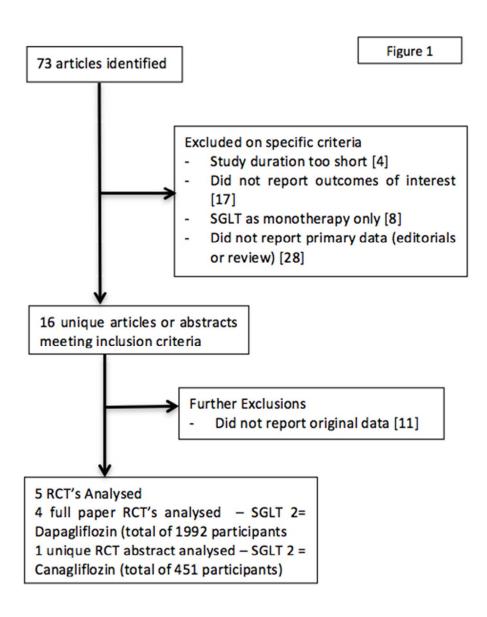
Page 1 of 2				
Section/topic	#	Checklist item	Reported on page #	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A	
Additional analyses	16	Describe methods of additional analyses (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).	6	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a	
DISCUSSION	•			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-11	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12	
FUNDING				
Funding 3	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

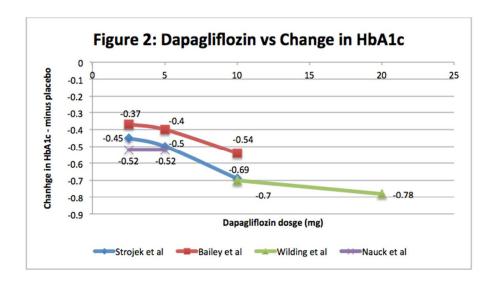
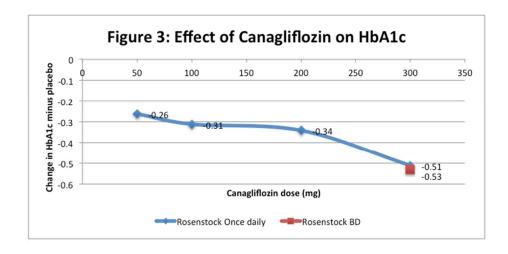
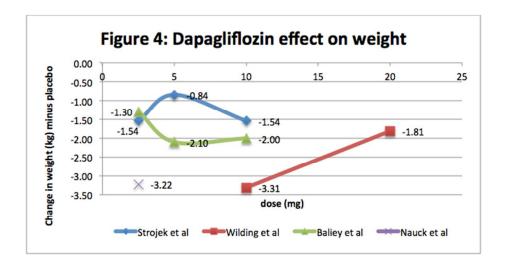


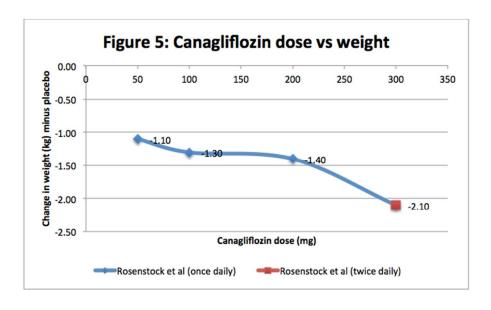
Figure showing reduction in HbA1c due to Dapagliflozin,



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
Primary Subject Heading :	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics, Evidence based practice
Keywords:	DIABETES & ENDOCRINOLOGY, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY

SCHOLARONE™ Manuscripts



47

Page 1 of 45

PRISMA 2009 Checklist Gill et al 2012

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TITLE			
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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
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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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PRISMA 2009 Checklist Gill et al 2012

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

assess safety in your results.	
2) The appendix table is okay but is so big and	A summary table with all the variables suggested
long that it does not	by the referee would be rather large, but we
provide a great summary of the articles within	take the point that a summary table would be
one viewing segment. I	useful. We have inserted one which is not quite
would recommend another summary table	as extensive as he suggested.
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.	
3) The discussion talks about the lack of long	We have added a paragraph on the FDA review.
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.	
4) I found the article results difficult to follow	Table added
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.	
Minor issues	
1) Abstract background: consider adding at the	We have added some text to the Objective in the
end of the sentence ",	Abstract to make it clear that our review is about
and little is known regarding their efficacy and	the use of these drugs in dual or triple therapy.
safety when used as	
dual or triple therapy for type 2 diabetes." This	
will help make it	

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.
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	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.
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	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	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

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

sentence on literature	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.	
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
error bars in figures 2 through 5	
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 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	

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.

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

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

between -0.37 and -0.78%	
-2nd paragraph - "no difference between dapagliflozin and glipizide" - Figure 2 appears to show a comparison of 2.5mg and 5mg. It is misleading to present data from an arm of the trial without dapagliflozin in this graph.	Accepted, and glipizide cross removed
There is no discussion of Figure 3 or Figure 5	Figure 3 now discussed. Figures 4 and 5 removed
Body weight - median weight reduction of - 2.33kg presented with confidence intervals. Is this mean rather than median? How was this	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 metanalysis. Data could then be presented in subgroups of dose. A summary statistic estimate need not be presented particularly if heterogeneity is	We remain convinced that a meta-analysis would not be appropriate.
arge, but should be considered. The authors are strongly urged to conduct a meta-analysis	
of their data.	

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

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Abstract

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

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

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

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

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

Results: four trials, published in full, assessed dapagliflozin and one, only available as a conference abstract, assessed canagliflozin. Trial quality appeared good for the published trials, however it could not be assessed for the conference abstract. Dapagliflozin reduced HbA1c, by 0.54% to 0.7% compared to placebo, but there was no difference compared to glipizide. Canagliflozin reduced HbA1c slightly more than sitagliptin (reductions of 0.71% and 0.56%). Both dapagliflozin and canagliflozin led to weight loss.

Limitations: trials were short term. No breakdown of relative effectiveness by duration was available. Data on canagliflozin is currently available from only one abstract. Costs of the drugs are not known so cost-effectiveness cannot be assessed. More data on safety are needed, with the FDA having concerns about breast and bladder cancers.

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

Introduction

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

It is estimated that 65% of people with diabetes will die as a result of cardiovascular complications (2,3), therefore anti-diabetic medications need to not only produce a reduction in HbA1c, but ideally also a reduction in cardiovascular disease mortality.

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

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

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

The key questions for this review are:

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

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

Methods

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

Participants:

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

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

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

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

Interventions:

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

Outcome measures.

The outcomes sought were:

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

Study Design

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

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

Search methods for identification of studies

We searched the following sources:

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

- Science Citation Index Expanded (SCI expanded)
- On-going Trials Registers:

- Clinical trials (www.clinicaltrials.gov)
- Current Control Trials (www.controlled-trials.com/)
- American Diabetes Association Conference Abstracts
- EASD Conference Abstracts
- Federal Drug Agency
- European Medicines Agency (EMEA)
- Scrutiny of bibliographies of retrieved papers

We searched for articles published since 2006, as this was the first recording of dapagliflozin on OVID. Initially returning 344 hits after the removal of duplications. An example of the SGLT2 dapagliflozin specific Medline search strategy performed via the OVID interface is listed below:

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

Reference lists of previous systematic reviews were checked for any trials not captured by the searches.

Data collection and analysis

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

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

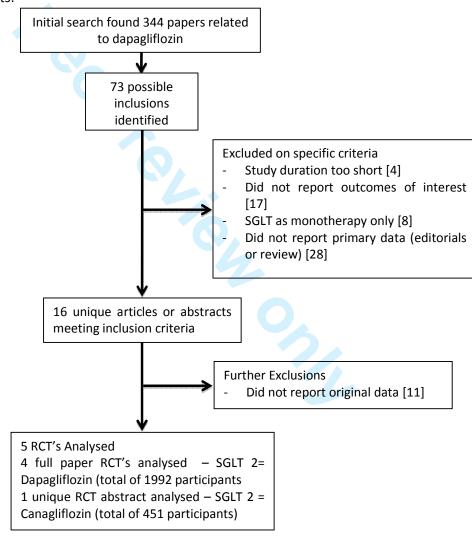
Data synthesis and analysis

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. Julilli	ialy of thats (ser	ected arms omy) and change in	HDAIC.	1
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^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.

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.

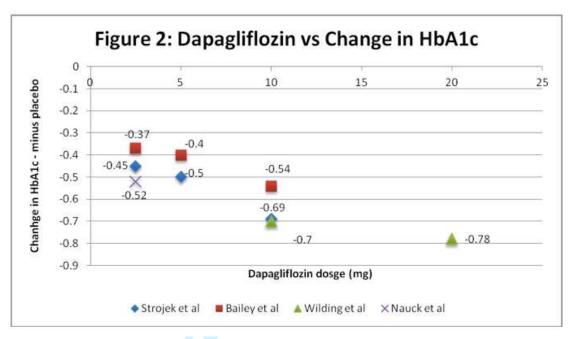
Table 2: Study Quality

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

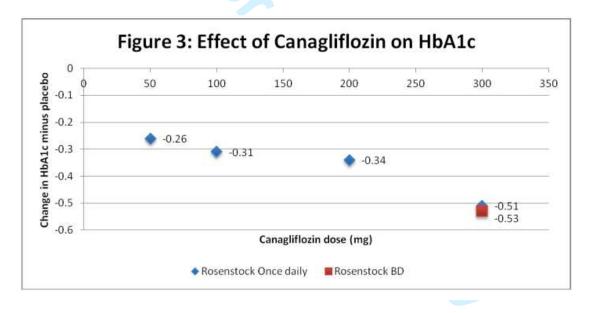
HbA1c Levels

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

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

References

1. Diabetes UK,

Diabetes in the UK 2010: Key statistics on Diabetes

http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf (Accessed October 1st 2011)

- 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 1st 2011)

7. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications.

Report of a WHO Consultation, WHO/NCD/NCS/99.2 (2000) http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf (Accessed Sept 20th 2011)

8. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF.

Effect of Dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial.

Lancet 2010; 375:2223-2233

 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 Dapa	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	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	102 week long-term study						
	Design: 4-arm RCT, double blind, placebo	controlled						
	Duimanu autamas Changa fram hasalina	in IIIh A 1 a at we als 2.4						
	Primary outcome: Change from baseline i	III HDATC 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							
	No. with baseline HbA1c of 9% or 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 of the control of th							
	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 tabl		indentification in the control of th	in assestanised to 1 1550mg				
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				
	Age: 53.7 SD 10.3 years	Age: 55.0 SD 9.3 years	Age: 54.3 SD 9.4 years	Age: 52.7 SD 9.9 years				
	Sex: 55% Male	Sex: 51% Male	Sex: 50% Male	Sex: 57% male				
	BMI (KG/M ²): 31.8 SD 5.3	BMI (KG/M²): 31.6 SD 4.8	BMI (KG/M²): 31.4 SD 5.0	BMI (KG/M²): 31.2 SD 5.1				
	HbA1c (%): 8.11% SD 0.96	HbA1c (%): 8.96% SD 2.39	HbA1c (%): 8.17% SD 1.0	HbA1c (%): 7.92% SD 0.82				
	Duration of Diabetes: 5.8 SD 5.1	Duration of Diabetes: 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): Systolic BP: 12		I): 8.66 SD 2.15 126.0 SD 15.9		
Outcome (chan	ge from baseline	e at study end)							
	Group 1 (n analysed=134): Placebo OD + metformin,		Group 2 (n= 135): 2.5mg dapagliflozin OD, metformin		Group 3 (n= 133 5mg dapaglifloz	3): in 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	
	Major hypoglycaemia = symptomatic episode, needing external assistance with following recovery, capillary glucose <3.0mmol/I)				GTI = Genital Tract Infection		Group 3 = n=	Group 2 = n=89 Group 3 = n=95 Group 4 = n=98	
	Group 1 (n an	alysed=134):	Group 2 (n= 135):		Group 3 (n= 133		Group 4 (n=	132):	
	Placebo OD +	metformin,	2.5mg dapagl	liflozin OD, metformin	ormin 5mg dapagliflozin OD, metformin		10mg dapagliflozin 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, HypoG n=5,		HypoT n=0, HypoG n=5		
	Diarrhoea n= 7		Diarrhoea n=	-	Diarrhoea n= 5		Diarrhoea n=		
	Back pain n= 7		Back pain n=		Back pain n= 3		Back pain n=		
	Nasopharyngi	tis n= 11	Nasopharyng	itis n= 12	Nasopharyngitis	s n=4	Nasopharyng	gitis n= 8	
	Cough n= 7 Influenza n= 1	0	Cough n= 4 Influenza n= 3	10	Cough n= 4		Cough n= 1 Influenza n=	0	
	Hypertension		Hypertension		Influenza n= 13		Hypertension		
	,,	ract Infection n= 10	/ .	ract Infection n= 5	Hypertension n= 4 Upper resp. Tract Infection n= 4			Tract Infection n= 3	
	Headache n= 6		Headache n=		Headache n= 1		Headache n=		
Safety Assessment	_	dverse events from the Medic				atient questionnaire and			

Dapagliflozin Vs Gli	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	34:[2015-2022]		SGLT2 Inhibitor + metformin vs metformin + glipizide						
Aim: Compare effic	acy, safety and tolerability of dapagliflozin with glipizide, in patien	nts with type 2 diabetes poorly controlled with monotherapy	1						
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 st	tudy							
	Design: 2-arm parallel group, RCT.								
	Primary outcome: Absolute change from baseline in HbA1c at week 52								
	Secondary outcomes:								
	- Change in total body weight								
	- Proportion with hypoglycaemic episode								
	- Proportion if ≥ 5% total weight loss.								
Participant	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 Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine ratio >203.4 mg/mmol; AST and/or ALT and/or creatine kinase ≥3 x upper limit of normal								
	total bilirubin >34 µmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSH; systolic blood pressure ≥180mmHg and/or diastolic blood								
	pressure ≥110 mmHg; significant other disease.								
Interventions	Intervention 1: 2.5mg dapagliflozin + metformin								
	Intervention 2: 5mg glipizide + metformin								
	Intervention 2: 5mg glipizide + metformin								
	Intervention 2: 5mg glipizide + metformin								
	Intervention 2: 5mg glipizide + metformin Lead in period: 2 weeks, single blind placebo lead in prior to ra	andomization.							
			tients maintained metformin						
Quality	Lead in period: 2 weeks, single blind placebo lead in prior to ra	y, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pa	tients maintained metformin						
·	Lead in period: 2 weeks, single blind placebo lead in prior to ra All groups: Patients randomly assigned to double blind therapy	y, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pa							
Participant	Lead in period: 2 weeks, single blind placebo lead in prior to ra All groups: Patients randomly assigned to double blind therapy Study Quality: medium – See Quality table for further information	y, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All partion							
Participant	Lead in period: 2 weeks, single blind placebo lead in prior to ra All groups: Patients randomly assigned to double blind therapy Study Quality: medium – See Quality table for further informat Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin Age: 58 SD 9 years	y, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pation Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin Age: 59 SD 10 years							
Participant	Lead in period: 2 weeks, single blind placebo lead in prior to ra All groups: Patients randomly assigned to double blind therapy Study Quality: medium – See Quality table for further informat Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin Age: 58 SD 9 years Sex: 55.3% Male	y, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pation Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin Age: 59 SD 10 years Sex: 54.9§% Male							
Participant	Lead in period: 2 weeks, single blind placebo lead in prior to ra All groups: Patients randomly assigned to double blind therapy Study Quality: medium – See Quality table for further informat 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	y, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pation 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	Lead in period: 2 weeks, single blind placebo lead in prior to ra All groups: Patients randomly assigned to double blind therapy Study Quality: medium – See Quality table for further informat Group 1 (start n= 406, analysed n=400): 2.5mg dapagliflozin + metformin Age: 58 SD 9 years Sex: 55.3% Male	y, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pation Group 2 (start n= 408, analysed n= 401) 5mg glipizide + metformin Age: 59 SD 10 years Sex: 54.9§% Male							
Quality Participant baseline data	Lead in period: 2 weeks, single blind placebo lead in prior to ra All groups: Patients randomly assigned to double blind therapy Study Quality: medium – See Quality table for further informat 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%%	y, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pation 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%							
Participant	Lead in period: 2 weeks, single blind placebo lead in prior to ra All groups: Patients randomly assigned to double blind therapy Study Quality: medium – See Quality table for further informat 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	y, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All pation 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							

	FPG (mmol/l): 9.0 SD 2.1		FPG (mmol/l): 9.1 SD 2.3			
Outcome (change	from baseline at study end)					
	Group 1 (start n= 406, analysed n=4 2.5mg dapagliflozin + metformin	00):	Group 2 (start n= 408, analysed n= 401): 5mg glipizide + metformin			
	Mean	Confidence (95%)	Mean	Confidence (95%)		
Δ HbA1c (%)	-0.52	-0.60 to -0.44	-0.52	-0.60 to -0.44		
Δ Weight (kg)	-3.22	-3.56 to -2.87	+1.44	+1.44		
Δ FPG (mmol/L)	-1.24	-1.42 to -1.07	-1.04	-1.22 to -0.98		
	Mean	SD	Mean	SD		
Δ SBP (mmHg)	-4.3	-	-+0.8	-		
HbA1c	-	-	-	-		
Adverse Events		mptomatic episode, capillary glucose	General events – where frequency is	At least one or more adverse event		
	<3.5mmol/l) Severe hypoglycaemia (HypoS) = sylassistance with following recovery, Other hypoglycaemia (HypoO) = sylconfirming		≥3% UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia other Group 1 = n=318 Group 2 = n=318 Group 2 = n=318 Group 2 = n=318 3 deaths in Dapagliflot 3 deaths in Glipizide group 3 d			
	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, i	n=0	UTI: n=26, GTI n = 11, HypoM n= 3 HypoS n= 147 HypoO, n=40 Events Leading to Discontinuation, n=6			
	Diarrhoea n= 19		Diarrhoea n= 26			
	Nausea n= 14 Vulvovaginal mycotic infection n= 1 Back pain n= 19 Nasopharyngitis n= 43 Cough n= 15	4	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= 11		Influenza n= 30 Pain in extremity n= 21			
	Upper resp. Tract Infection n= 24 Headache n= 21 Hypertension n= 30		Upper resp. Tract Infection n= 17 Headache n= 17 Hypertension n= 35			
Safety Assessment	, ·	ne Medical Dictionary or Regulatory Activit	ties (MedDRA v12.1) via patient questionnaire	and active questioning during visits		

nibitor of sodium glucose co-transporter 2, improves glycaemic control, lowers body weight, and improves beta cell function in 2 diabetes on background metformin						
S3:[S349]	Placebo + metformin					
3.(33-73)	Vs					
	SGLT2 Inhibitor + metformin OD					
	Vs					
	SGLT2 inhibitor BD + metformin OD					
	Vs					
	sitaglipitin OD + metformin					
ety, tolerability and efficacy of an alternative SGLT2 inhibitor Canagliflozin and remaining beta cell function, in DM type 2 patients						
a monotherapy.	who have madequate grycaernic control					
ulti Centre: no comment in abstract						
rration of intervention: 12 weeks						
Duration of run in: no comment in abstract						
llow-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						
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						
udy Quality: Medium – See Quality table for further information						
7 study groups, each group contained 64-65 patients, individual group numbers not given in abstract						
selines across all groups only given as overall average						
e: 53						
x: -						
лі (KG/M²): 31.5						
\1c (%): 7.7%						
rration of Diabetes: -						
G (mmol/l): 9.0						
stolic BP: -						
Stolic Di						
G (m	mol/I): 9.0					

	Group 1 placeb	o + metformin	Group 2 canage Metformin	gliflozin 50mg +	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)	-	100	-	-	-	-	-	-	
HbA1c	7.5	0.96	7.2	0.88	7.1	0.85	6.9	0.68	
	Group 5 canagl	iflozin 300mg + metformin	Group 6 canag	gliflozin 300mg BD +	Group 7 sitagli	iptin + metformin			
	Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)			
Δ HbA1c (%)	-0.71	-	-0.73	-	-0.56	-			
Δ Weight (kg)	-2.3	-	-2.3	/ /-	+0.4	-]		
Δ FPG (mmol/L)	-1.8	-	-1.7		-1.0	-	-		
	Mean	SD	Mean	SD	Mean	SD			
Δ SBP (mmHg)	-	-	-	- (4)	-	-			
HbA1c	6.8	0.82	6.8	0.72	6.9	0.92	†		
Adverse Events		more adverse event balance							
Specific	Genital tract in		UTI		Hypoglycaem	ia (not defined in			
Events	3-8% canagliflo	zin arms	3-9% canaglif	lozin arms	abstract)				
	2% placebo		6% placebo		0-6% canagliflozin arms				
	2% sitagliptin		2% sitagliptin		2% placebo 5% sitagliptin	9/2/			
	All AE were seen to be non-dose dependent								
	After 12 weeks	no "safety signals" (not defi	ned in abstract)	in lab studies, ECG or vit	al signs were see	en in Canagliflozin arms			
	Similar inciden	ces of discontinuation due to	adverse events,	, although number not s	ecified				
	Number of sev	ere adverse events not given							
Safety	Assessed via ad	lverse events from the Medic	al Dictionary or R	Regulatory Activities (Med	IDRA v12.1) via p	patient questionnaire and act	ive questionin	g during visits	

	KH, Hruba V, Elze M, Langkilde AM, Parikh S. liflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, dou	Funding source: Astra-Zeneca and Bristol-Myers-Squibb					
	controlled trial.	bie- Bristoi-iviyers-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 with inadequately lphonylurea monotherapy	controlled type 2 diabetes who had been					
Study	Multi Centre: 84 sites across 7 countries						
Particulars	Duration of intervention: 52 weeks						
i ai ticulai s	Duration of run in: 2 weeks						
	Follow-up: on completion of 52 weeks, a 156 week long-term study						
	Design: 2-arm parallel group, double-blind RCT						
	Primary outcome: Absolute HbA1c change from baseline to week 24						
	Secondary outcomes:						
	- Total body weight after 24 weeks						
	- Change from baseline after week 24 in post challenge plasma glucose (2hrs) following oral glucose tolerance						
	- Proportion of patients with HBA1c <7% after 24 weeks						
	Total body weight from baseline if BMI ≥27kg/m ²						
	FPG from baseline after 24weeks						
Participant Criteria	N: 592 analyzed						
	Inclusion criteria: Participants aged 18 years and older; inadequately controlled type 2 diabetes, BMI ≤45kg/m², HbA1c of ≥7 to least half maximum dose (max 4 mg) for at least 8 weeks prior to enrolment); fasting C-peptide ≥0.33 nmol/ml, fasting plasma						
	Exclusion criteria: creatinine clearance <50 mL/minor serum creatinine >177 μmol/L; urine albumin: creatinine ratio >203.4 mg/mmol; AST and/or ALT and/or creatine						
	kinase ≥3 x upper limit of normal; total bilirubin >34 µmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/dL for women; abnormal TSH; SBP ≥180 mmHg and/or DBP ≥110						
	mmHg. Any significant other systemic disease						
Interventions	Intervention 1: placebo plus 4 mg/day glimepiride						
	Intervention 2: 2.5 mg/day dapagliflozin plus 4 mg/day glimepiride						
	Intervention 3: 5 mg/day dapagliflozin plus 4 mg/day glimepiride						
	Intervention 4: 10 mg/day dapagliflozin plus 4 mg/day glimepiride						
	Lead in period: 1 week for inclusion/exclusion review for those switched to 4 mg/day glimepiride						
	All groups: dapagliflozin double-blind, glimepiride open label; glimepiride allowed to be down-titrated to 2 mg/day or disconti titration allowed; in case of inadequate glycaemic control, patients could receive open-label rescue therapy of metformin, piog						
	dietary and lifestyle counseling and patients with BMI ≥27 kg/m ² received advice regarding reducing caloric intake and increas						
Quality	Study Quality: Medium – See Quality table for further information						
Participant	Group 1 (n= 146) Group 2 (n= 154) Group 3 (n= 145)	Group 4 (n= 151)					

baseline data	Placebo + glime	piride	2.5mg dapagliflo	zin + glimepiride	5mg dapagliflozin	ı + glimepiride	10mg dapagliflozin + glimepiride		
	Age (years): 60. Sex: 49% male BMI (kg/m²) ≥ 25 kg/m²: 86.	3 SD 10.16	Age (years): 59.9 Sex: 50% male BMI (kg/m²) ≥ 25 kg/m²: 84.4	9.3 SD 10.14	Age (years): 60.2 SD 9.73 Sex: 50% male BMI (kg/m²) ≥ 25 kg/m²: 78%		Age (years): 58.9 SD 8.32 Sex: 43.7% male BMI (kg/m²) ≥ 25 kg/m²: 79.4%		
	≥ 30 kg/m ² : 45.5% HbA1c (%): 8.15 SD 0.74 Duration of diabetes (years): 7.4SD 5.7 FPG (mmol/L): 9.58 SD 2.07 Systolic BP (mmHg): 133.3		HbA1c (%): 8.11, SD 0.75 Duration of diabetes (years): 7.7 SD 6.0		≥ 30 kg/m ² : 50% HbA1c (%): 8.12 SD 0.78 Duration of diabetes (years): 7.4 SD 5.7 FPG (mmol/L): 9.68 SD 2.12 Systolic BP (mmHg): 130.9		≥ 30 kg/m ² : 45.% HbA1c (%): 8.07 SD 0.79 Duration of diabetes (years): 7.2 SD 5.5 FPG (mmol/L): 9.55 SD 2.04 Systolic BP (mmHg): 133.8 SD 15		
Outcome (chang	ge from baseline a	at study end)							
	Group 1 (n= 146 Placebo + glime		Group 2 (n= 154) 2.5mg dapagliflo		Group 3 (n= 145) 5mg dapagliflozin		Group 4 (n= 10mg dapagl	151) iflozin + glimepiride	
	Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)	
Δ from baseline HbA1c (%)	-0.13	-	-0.58	-0.61 to -0.27	-0.63	-0.67 to -0.32	-0.82	-0.86 to -0.51	
Δ from baseline Weight (kg)	-0.72	-	-1.18	-1.08 to +0.15	-1.56	-1.47 to -0.21	-2.26	-2.17 to -0.92	
Δ from baseline FPG (mmol/L)	-0.33	-	-2.08	-2.50 to -1.00	-1.78	-2.20 to -0.68	-1.94	-2.34 to 0.87	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Absolute Δ SBP from placebo (mmHg)	-1.20	-	-4.7	-6.1 to -0.9	-4.0	-5.5 to -0.2	-3.8	-6.4 to -1.2	
HbA1c	-	-	-	-	-	-	-	-	
Adverse Events	nts General events – where frequency is ≥3% i UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia		n any group		Hypoglycaemia d <70mg/dl)	efined as blood sugar	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 3 (n= 145) T death in Dapagi				

	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 M	ledical Dictionary or Regulatory Activities (I	MedDRA v12.1) via patient questionnaire a	and active questioning during visits
Assessment				

Wilding JPH, Norwo	ood P, T'joen C, Bastien A, List JF, Fiedorek FT.	Funding source: Astra-Zeneca and
A Study of Dapaglit independent treatr	Bristol-Myers-Squibb	
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 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 kinase ≥3 times the upper limits	mits 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	ma danaaliflazin onco daily plu	ic inculin concitizor a	and inculin as in intervention	1			
	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 loc period there were no dose adjustments to OADs; insulin could be down-titrated in patients at risk of hypoglycaemia							
	•	,		wn-titrated in patients at risk	of hypoglycaemia			
	<u> </u>	21 day to establish reduced in						
Quality		m – See Quality table for further						
Participant	Group 1 (n analysed=	•	Group 2 (n= 23):		Group 3 (n= 23):			
baseline data	Placebo, OADs + insu	•	10mg dapagliflozin,		0 1 0	n OD, OADs + insulin,		
	Age (years): 58.4 SD 6	5.5	Age (years): 55.7 SE	9.2	Age (years): 56.1	SD 10.6		
	Sex: 69.6% male		Sex: 54.2% male		Sex: 54.2% male			
	BMI (kg/m²): 34.8 SD		BMI (kg/m²): 35.5 S		BMI (kg/m ²): 36.2			
	HbA1c (%): 8.40% SD		HbA1c (%): 8.4% SD		HbA1c (%):8.5% S			
	Duration of diabetes			es (years): 11.8 SD 5.8		etes (years): 11.3 SD 5.6		
	FPG (mmol/L): 9.22 S		FPG (mmol/L): 8.67			FPG (mmol/L): 8.98 SD 3.06		
	Systolic BP (mmHg):		Systolic BP (mmHg)	: n/a	Systolic BP (mmHg): n/a			
Outcome (change	from baseline at study e							
	Group 1 (n analysed=19):		Group 2 (n= 23):		Group 3 (n= 23):			
	Placebo, OADs + insu	· · · · · · · · · · · · · · · · · · ·	10mg dapagliflozin,		20mg dapagliflozi	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 hypoglycaemic	a = symptomatic episode,	General events – w	here frequency is >5%	At least one or m	ore adverse event		
Auverse Liverits	capillary glucose <3.5		UTI = Urinary Tract Infection		Group 1 = n=15	ore udverse event		
	, , ,	a = symptomatic episode,	GTI = Genital Tract Infection		•	Group 2 = n=18		
		stance with following recovery,	HypoT = Hypotension		Group 3 = n=16			
	capillary glucose <3.0		HypoG = Hypoglycaemia		One patient in each group discontinued due to			
	capillary gracose 15.0		Trypod - Trypogrycuciniu		adverse effects			
Specific Events	Group 1 (n analysed=	19):	Group 2 (n= 23):		Group 3 (n= 23):			
	Placebo, OADs + insu	= -	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=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 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
Safety Assessment	Assessed via adverse events from the Medic	cal Dictionary or Regulatory Activities (MedDRA v12.1) via	Upper resp. Tract Infection n= 1 patient questionnaire and active questioning during visits

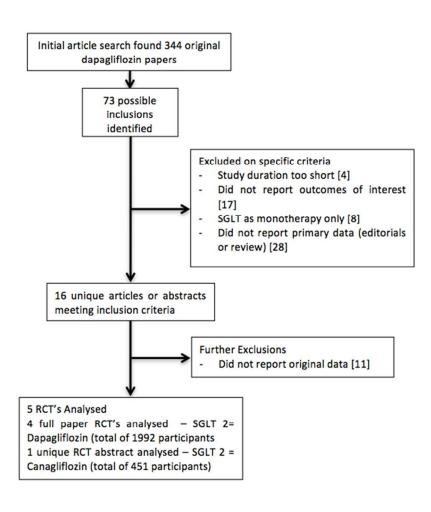


Image of figure 1

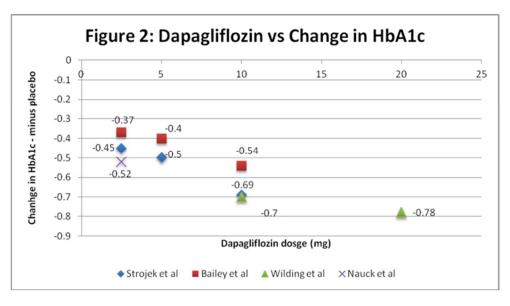
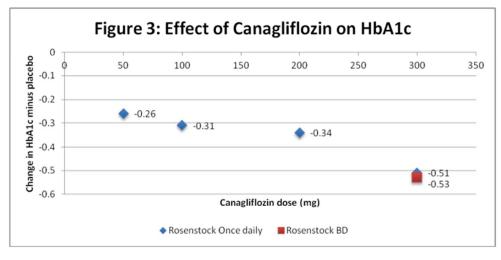


image of figure 2





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

Journal:	BMJ Open
Manuscript ID:	bmjopen-2012-001007.R2
Article Type:	Research
Date Submitted by the Author:	21-Jun-2012
Complete List of Authors:	Waugh, Norman; Warwick University, Division of Health Sciences Clar, Christine Gill, James; University of Wariwick, Division of Health Sciences; University Hospitals Coventry and Warwickshire, Endocrinology Court, Rachel; Warwick University, Division of Health Sciences
Primary Subject Heading :	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics, Evidence based practice
Keywords:	DIABETES & ENDOCRINOLOGY, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY

SCHOLARONE™ Manuscripts

47



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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary 3	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
B 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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Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.	Synthesis of results 14
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	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).	6		
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a		
DISCUSSION					
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-11		
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12		
B Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12		
FUNDING	1				
p 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.	
autilois.	
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	
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	
	<u>L</u>

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	We have added a paragraph on the FDA review.
areas to address potential concerns of specific adverse effects. 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.
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	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

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

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

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

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

inclusion criteria.	
The results of this systematic review have been presented in graphical format, with data points from all included studies plotted together. In this format it is difficult to interpret the data, though the authors have attempted to do this through narrative and overall statements. The authors state that a meta-analysis was not conducted because of the small number and heterogeneity of the trials. As 5 trials have been included in the review, and each of these report outcomes which can be compared, a meta-analysis could be conducted. The authors throughout the paper make summary statements about the results, however the method of analysis used by the investigators is not appropriate to draw these conclusions. A meta-analysis should be conducted and would substantially improve the	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
paper.	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	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.

	1
optimum dosage of 10-20mg.	
The presentation of the results in this review needs to be revised. This could be achieved by conducting a metanalysis. Data could then be presented in subgroups of dose. A summary statistic estimate need not be presented particularly if heterogeneity is arge, 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.
tileli 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.

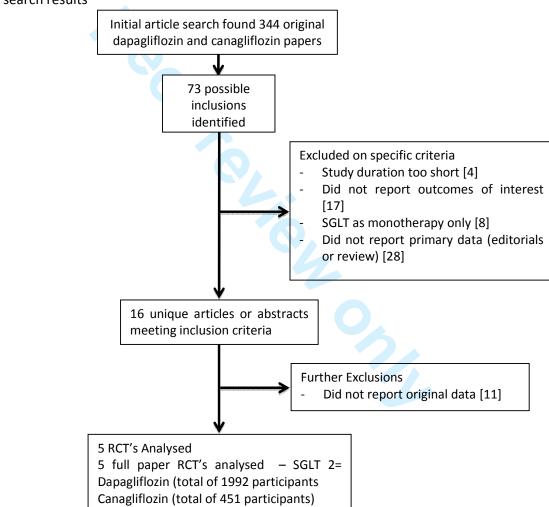
Data synthesis and analysis

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 32.7kg/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.

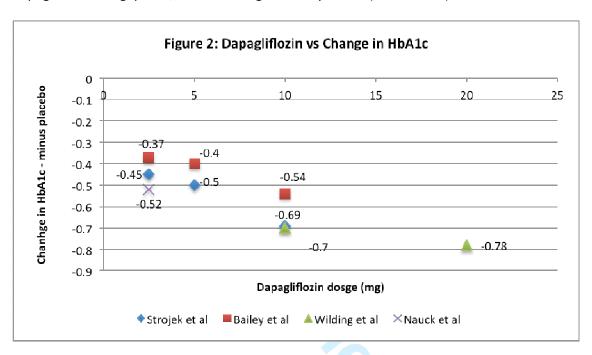
study	SGLT2 inhibitor	Comparator	Baseline HbA1c (SD)	Change in HbA1c (95% CI)	Difference
Bailey 2010	Dapaglifozin 10mg + metformin N=122	Placebo + metformin N= 134	Dap 7.9% (1.0) Pbo 8.1% (0.98)	Dap -0.84% (0.70-0.98 Pbo -0.3% (0.16-0.44)	0.54%
Nauck 2011	Dapagliflozin 2.5mg + metformin N= 406	Glipizide 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

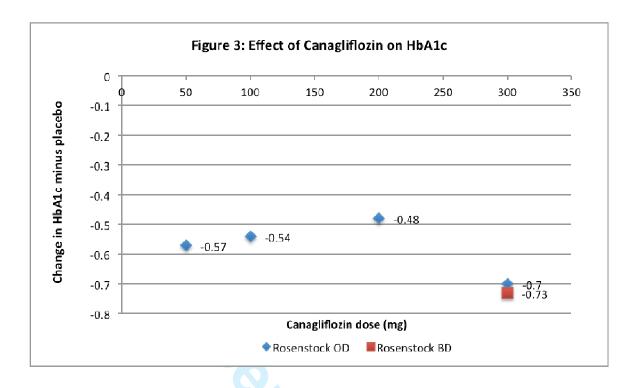
HbA1c Levels

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 1st 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 1st 2011)

7. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications.

Report of a WHO Consultation, WHO/NCD/NCS/99.2 (2000) http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf (Accessed Sept 20th 2011)

8. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF.

Effect of Dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial.

Lancet 2010; 375:2223-2233

 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, placebocontrolled 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

g Administration in the Enuc. 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 who	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 dial	etes 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	controlled						
	Primary outcome: Change from baseline in	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 Proportion of patients achieving a therapeutic HbA1c, and 							
	Glucose concentration Total bodyweight							
	 No. with baseline HbA1c of 9% o 	r more. • Change from baseline in	oodyweight, 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 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		ndomised successful completion. Metform	in dose stabilised to >1500mg				
Quality	Study Quality: medium – See Quality table							
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				
	Age: 53.7 SD 10.3 years	Age: 55.0 SD 9.3 years	Age: 54.3 SD 9.4 years	Age: 52.7 SD 9.9 years				
	Sex: 55% Male	Sex: 51% Male	Sex: 50% Male	Sex: 57% male				
	BMI (KG/M²): 31.8 SD 5.3	BMI (KG/M²): 31.6 SD 4.8	BMI (KG/M²): 31.4 SD 5.0	BMI (KG/M ²): 31.2 SD 5.1				
	HbA1c (%): 8.11% SD 0.96	HbA1c (%): 8.96% SD 2.39	HbA1c (%): 8.17% SD 1.0	HbA1c (%): 7.92% SD 0.82				
	Duration of Diabetes: 5.8 SD 5.1	Duration of Diabetes: 6.0 SD 6.2	Duration of Diabetes: 6.4 SD 5.8	Duration of Diabetes: 6.1 SD 5.4				

Assessment

FPG (mmol/l): 9.19 SD 2.57 Systolic BP: 127.7 SD 14.6		/I): 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		
e at study end)							
lysed=134): metformin,	Group 2 (n= 2.5mg dapa	= 135): gliflozin OD, metformin	Group 3 (n= 133 5mg dapaglifloz	3): in OD, metformin	Group 4 (n= 1 10mg dapagl		
Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)	
-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	
-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	
-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	
SD	Mean	SD	Mean	SD	Mean	SD	
1.20	-2.10	1.10	-4.3	1.30	-5.10	1.30	
1.18	7.34	0.93	7.42	0.94	7.13	0.94	
ycaemia = symptomatic episc very, capillary glucose <3.0m		ternal assistance with	UTI = Urinary Tr GTI = Genital Tr HypoT = Hypote HypoG = Hypogl	act Infection ension	Group 2 = n=89 Group 3 = n=95 Group 4 = n=98		
alysed=134): metformin,	Group 2 (n= 135): 2.5mg dapagliflozin OD, metformin		Group 3 (n= 133): 5mg dapagliflozin OD, metformin		Group 4 (n= 132): 10mg dapagliflozin OD,		
I n = 7, /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	
7	Diarrhoea n		Diarrhoea n= 5		Diarrhoea n= 10		
•	Back pain n	= 5	Back pain n= 3		Back pain n=	10	
tis n= 11	Nasopharyn	ngitis n= 12	Nasopharyngitis	s n=4	Nasopharyng	ritis n= 8	
	Cough n= 4		Cough n= 4		Cough n= 1		
0	Influenza n=	-	Influenza n= 13		Influenza n=		
n= 6	Hypertensio		Hypertension n		Hypertension		
act Infection n= 10		Tract Infection n= 5		ct Infection n= 4		Fract Infection n= 3	
5		Headache n	Headache n= 4	Headache n= 4 Headache n= 1	Headache n= 4 Headache n= 1		

BMJ Open

Page 34 of 47

•	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 inad 34-(2015-2022)	equate glycaemic control with Metformin	Funding source: Astra-Zeneca and Bristol-Myers-Squibb			
Diabetes care 2011.	J4.[2013 2022]	SGLT2 Inhibitor + metformin vs metformin + glipizide				
Aim: Compare effic	acy, safety and tolerability of dapagliflozin with glipizide, in patients with ty	pe 2 diabetes poorly controlled with monotherapy	У			
Study Particulars	Multi Centre: 95 sites across 10 countries World-wide Duration of intervention: 52 weeks Duration of run in: 2 weeks Followup: on completion of 52 weeks, a 156 week long-term study					
	Design: 2-arm parallel group, RCT.					
	Primary outcome: Absolute change from baseline in HbA1c at week 52					
	Secondary outcomes:					
	- Change in total body weight					
	 - Proportion with hypoglycaemic episode - Proportion if ≥ 5% total weight loss. 					
Participant	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: creatotal bilirubin >34 μmol/L; hemoglobin (Hb) ≤11 g/dL for men and ≤10 g/pressure ≥110 mmHg; significant other disease.					
Interventions	Intervention 1: 2.5mg dapagliflozin + metformin Intervention 2: 5mg glipizide + metformin					
	Lead in period: 2 weeks, single blind placebo lead in prior to randomization.					
	All groups: Patients randomly assigned to double blind therapy, either, placebo, 2.5mg dapagliflozin or glipizide 5mg. All patients maintained metformin					
Quality	Study Quality: medium – See Quality table for further information					
Participant	Group 1 (start n= 406, analysed n=400):	Group 2 (start n= 408, analysed n= 401):			
baseline data	2.5mg dapagliflozin + metformin	5mg glipizide + metformin				
	Age: 58 SD 9 years	Age: 59 SD 10 years				
	Sex: 55.3% Male	Sex: 54.9§% Male				
	BMI (KG/M²): 31.7 SD 5.1	BMI (KG/M²): 31.2 SD 5.1				
	≥ 25 kg/m²: 95%%	≥ 25 kg/m² : 90.7%				
	≥ 30 kg/m²: 57%	≥ 30 kg/m²: 55.4%				
	HbA1c (%): 7.7% SD 0.9	HbA1c (%): 7.7% SD 0.9				
	Duration of Diabetes: 6 SD 5	Duration of Diabetes: 7 SD 6				

	FPG (mmol/l): 9.0 SD 2.1		FPG (mmol/l): 9.1 SD 2.3	FPG (mmol/l): 9.1 SD 2.3			
Outcome (change	from baseline at study end)						
	Group 1 (start n= 406, analysed r	=400):	Group 2 (start n= 408, analysed n= 401):				
	2.5mg dapagliflozin + metformin Mean Confidence (95%)		5mg glipizide + metformin				
			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	1-	<u> </u>	-				
Adverse Events	Minor hypoglycaemia (HypoM) = <3.5mmol/l)	symptomatic episode, capillary glucose	General events – where frequency is ≥3%	At least one or more adverse event Group 1 = n=318			
		symptomatic episode, needing external	UTI = Urinary Tract Infection GTI = Genital Tract Infection	Group 2 = n=318			
	_	symptoms, but without measurement	HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild)	No deaths in Dapagliflozin group 3 deaths in Glipizide group			
	Group 1		HypoO = Hypoglycaemia other Group 2	Group 2			
Specific Events	UTI: n=44, GTI n = 50,		UTI: n=26, GTI n = 11,				
Specific Events	HypoM n= 0 HypoS n= 7		HypoM n= 3 HypoS n= 147				
	HypoO, n=7		HypoO, n=40				
	Events Leading to Discontinuation	n. n=0	Events Leading to Discontinuation, n=6 Diarrhoea n= 26				
	Diarrhoea n= 19	y					
	Nausea n= 14		Nausea n= 15				
	Vulvovaginal mycotic infection 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				
	Influenza n= 30		Influenza n= 30				
	Pain in extremity n= 11		Pain in extremity n= 21				
	Upper resp. Tract Infection n= 24		Upper resp. Tract Infection n= 17				
	Headache n= 21		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 B	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 Johnso				
Diabetes Care J	une 2012 vol. 35 no. 6 1232-1238	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 patient n as a monotherapy.					
Study	Multi Centre: 12 countries at 85 sites					
Particulars	Duration of intervention: 12 weeks Duration of run in: 4 week					
	Followup: 2 week					
	Design: 7-arm parallel group, RCT. Double blind, placebo controlled trial looking at metformin, canagliflozin 50, 100, 200, 300mg OD and 300mg BD, and sitaglipitin 100mg					
	Primary outcome: Change from baseline in HbA1c					
	Secondary outcomes:					
	Change in fasting plasma glucose at week 12, change in weight, overnight glucose-to-creatinine ratio, change in proportion of subjudges. 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 inadequate glycaemic control using metformin monotherapy, stable body weight, BMI 25-45, serum creatinine <1.5mg/dl for men, <1.4mg/dl for women					
	Exclusion criteria (taken from paper): HbA1c ≥10.6%, metformin dose of ≤1500mg/day, unstable body weight, BMI≤25 ≥45, serum	n creatinine ≥1.4				
	Lead in period: 3-4 weeks					
Quality	Study Quality: Medium – See Quality table for further information					
Participant	Age: 53					
baseline data	Sex: male 52%					
	BMI (KG/M ²): 31.5					
	HA1c (%): 7.7%					
	Duration of Diabetes: -					
	FPG (mmol/l): 9.0					
	Systolic BP:					
Outcome (street						
Outcome (char	ge from baseline at study end)					

	Group 1 placebo + mo	etformin (n=55)	Group 2 o	_	ozin 50mg +	Group 3 canag (n=59)	liflozin 100m	g + metformin	Group 4 canagliflozin 200mg + metformin (n=56)	
	Mean	Confidence (95%)	Mean	11 (11–33)	Confidence (95%)	Mean	Cor	nfidence (95%)	Mean	Confidence (95%)
Δ HbA1c (%)	-0.22	-	-0.79		-	-0.76	-	machee (55%)	-0.70	-
Δ Weight (kg)	-1.1	_	-1.2		_	-1.5	_		-1.6	-
Δ FPG	+0.19	_	-0.9		_	-1.4	-		-1.8	_
(mmol/L)			0.5			1			1.0	
	Mean	SD	Mean		SD	Mean	SD		Mean	SD
ΔSBP	-1.3	1.5	-0.9		1.7	+1.0	1.3		-2.1	1.8
(mmHg)										
HbA1c	7.5	0.96	7.2		0.88	7.1	0.8	5	6.9	0.68
	Group 5 canagliflozin	300mg + metformin	Group 6	canaglifle	ozin 300mg BD +	Group 7 sitagli	ptin + metfo	rmin		
	(n=56)		metformin (n=57)		(n=60)					
	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	-1.8	-	-1.7		-	-0.69	-			
(mmol/L)										
	Mean	SD	Mean		SD	Mean	SD			
ΔSBP	-4.9	1.5	-3.6		1.4	-0.8	1.4			
(mmHg)										
HbA1c	6.8	0.82	6.8		0.72	6.9	0.92	2		
Adverse Events	episode, capillary glud Severe hypoglycaem episode, needing exter recovery, capillary glu	ia (HypoS) = symptomati ernal assistance with foll ucose <3.0mmol/l) a (HypoO) = symptoms, b	ic owing	UTI = I	ral events – where fre Urinary 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			Group 4	
Events	UTI: n=4, GTI n = 1		UTI: n=3,		•	UTI: n=2, GTI n	,		UTI: n=6, GT	
	Events Leading to Dis	continuation, n=1			Discontinuation,	Events Leading	to Discontir	uation, n=3		ng to Discontinuation, n=1
	Hypo = 1		n=1 Hypo			Hypo = 1			Hypo = 4	
	Headache n= 2		Headache			Headache n= 5			Headache n	-
	Vulvovaginal mycotic	intection n= 0	_	-	otic infection n= 4	Vulvovaginal m	nycotic infect	ion n= 2	_	mycotic infection n= 4
	Nausea n= 0		Nausea n		- F	Nausea n= 1	.t 0		Nausea n= 1	
	Nasopharyngitis n= 2		Nasophar		1= 5	Nasopharyngit			Nasopharyn	
	Diarrhoea n= 2		Diarrhoea			Diarrhoea n= 1			Diarrhoea n	
	Pollakiuria n = 1		Pollakiuria	a n = 1		Pollakiuria n =	5		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	al Dictionary or Regulatory Activties (Med	DRA v12.1) via patient questionnaire and ac	tive questioning during visits			

Strojek K, Yoon	KH, Hruba V, Elze M, Langkilde AM, Parikh S.	Funding source: Astra-Zeneca and
Effect of Dapag	liflozin 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
Aim: To determ	ine efficacy, safety and tolerability of dapagliflozin treatment, as an add-on therapy to glimepiride, in patients with inadequately contro	olled type 2 diabetes who had been
treated with su	lphonylurea monotherapy	
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 R Primary outcome: Absolute HbA1c change fr						
	Secondary outcomes: - Total body weight after 24 weeks - Change from baseline after week 2 - Proportion of patients with HBA1c	4 in post challenge plasma glucose (2hrs <7% after 24 weeks) following oral glucose tolerance				
	Total body weight from baseline if - FPG from baseline after 24weeks	BMI ≥27kg/m ²					
Participant Criteria	N: 592 analyzed						
	Inclusion criteria: Participants aged 18 years least half maximum dose (max 4 mg) for at least half maximum dose (
	Exclusion criteria: creatinine clearance <50 r kinase ≥3 x upper limit of normal; total biliru mmHg. Any significant other systemic diseas	bin >34 μmol/L; hemoglobin (Hb) ≤11 g/d					
Interventions	Intervention 1: placebo plus 4 mg/day glimepiride Intervention 2: 2.5 mg/day dapagliflozin plus 4 mg/day glimepiride Intervention 3: 5 mg/day dapagliflozin plus 4 mg/day glimepiride Intervention 4: 10 mg/day dapagliflozin plus 4 mg/day glimepiride						
	Lead in period: 1 week for inclusion/exclusion review for those switched to 4 mg/day glimepiride						
	All groups: dapagliflozin double-blind, glimepiride open label; glimepiride allowed to be down-titrated to 2 mg/day or discontinued in case of hypoglycaemia, no uptitration allowed; in case of inadequate glycaemic control, patients could receive open-label rescue therapy of metformin, pioglitazone or rosiglitazone; all patients received dietary and lifestyle counseling and patients with BMI ≥27 kg/m² received advice regarding reducing caloric intake and increasing physical activity						
Quality	Study Quality: Medium – See Quality table for	or further information					
Participant	Group 1 (n= 146)	Group 2 (n= 154)	Group 3 (n= 145)	Group 4 (n= 151)			
baseline data	Placebo + glimepiride Age (years): 60.3 SD 10.16 Sex: 49% male BMI (kg/m²) ≥ 25 kg/m²: 86.2%	2.5mg dapagliflozin + glimepiride Age (years): 59.9.3 SD 10.14 Sex: 50% male BMI (kg/m²) ≥ 25 kg/m²: 84.4%	5mg dapagliflozin + glimepiride Age (years): 60.2 SD 9.73 Sex: 50% male BMI (kg/m²) ≥ 25 kg/m²: 78%	10mg dapagliflozin + glimepiride Age (years): 58.9 SD 8.32 Sex: 43.7% male BMI (kg/m²) ≥ 25 kg/m²: 79.4%			
	≥ 30 kg/m²: 45.5% HbA1c (%): 8.15 SD 0.74 Duration of diabetes (years): 7.4SD 5.7 FPG (mmol/L): 9.58 SD 2.07 Systolic BP (mmHg): 133.3	≥ 30 kg/m²: 48% HbA1c (%): 8.11, SD 0.75 Duration of diabetes (years): 7.7 SD 6.0 FPG (mmol/L): 9.56, SD 2.13 Systolic BP (mmHg): 134.6	≥ 30 kg/m²: 50% HbA1c (%): 8.12 SD 0.78 Duration of diabetes (years): 7.4 SD 5.7 FPG (mmol/L): 9.68 SD 2.12 Systolic BP (mmHg): 130.9	≥ 30 kg/m ² : 45.% HbA1c (%): 8.07 SD 0.79 Duration of diabetes (years): 7.2 SD 5.5 FPG (mmol/L): 9.55 SD 2.04 Systolic BP (mmHg): 133.8 SD 15			

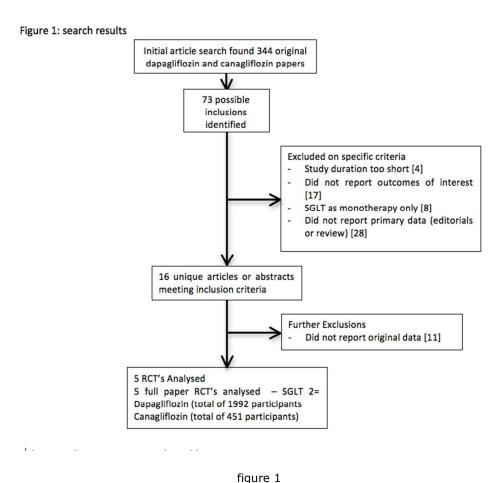
	Group 1 (n= 146	Group 1 (n= 146)		Group 2 (n= 154)		Group 3 (n= 145)		151)
	Placebo + glime	piride	2.5mg dapagli	2.5mg dapagliflozin + glimepiride		5mg dapagliflozin + glimepiride		iflozin + glimepiride
	Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)	Mean	Confidence (95%)
Δ from baseline 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	-	-	-	-	-	-	-	-
	UTI = Urinary T GTI = Genital Ti Hypo = Hypogly	ract Infection			<70mg/dl)			:80 :70 :76 apagliflozin 2.5mg
			T					apagliflozin 10mg
	Group 1 (n= 14	=	Group 2 (n= 1	•	Group 3 (n= 14		Group 4 (n=	•
Specific Events	Placebo + glime UTI: n=9, GTI n	•		flozin + glimepiride		zin + glimepiride	10mg dapagliflozin + glimepiride	
Specific Everits	≥ 1Hypo n= 7	- ı,	UTI: n=6, GTI n = 6, ≥ 1Hypo n= 11		UTI: n=10, GTI n = 9, ≥ 1Hypo n= 11		UTI: n=8, GTI n = 10, ≥ 1Hypo n= 12	
	Bronchitis n= 4		Bronchitis n= 2		Diarrhoea n= 2		Bronchitis n=	
	Diarrhoea n= 5		Diarrhoea n= 4		Back pain n= 3		Diarrhoea n=	-
					Nasopharyngiti		Back pain n=	
	Back pain n= 4		Nasopharyngitis n= 4 Nasopharyngitis n= 3				Nasopharyngitis n= 5	
	Back pain n= 4	s n= 4			Arthralgia n= 0		Nasopharyng	gitis n= 5
	Back pain n= 4	s n= 4		tis n= 3		act Infection n= 6	Nasopharyng Arthralgia n=	•
	Back pain n= 4 Nasopharyngiti Arthralgia n= 4	is n= 4 act Infection n= 4	Nasopharyngi Arthralgia n= 6	tis n= 3		act Infection n= 6	Arthralgia n=	•

	ood P, T'joen C, Bastien A, List JF, Fiedorek FT.	oses of Insulin Plus Insulin Sensitizers. Applicability of a no	Funding source: Astra-Zeneca and byel insulin- Bristol-Myers-Squibb			
independent treatn		,				
Diabetes care 2009			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 do	oses 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 lor	g-term study				
	Design: 2-arm parallel group, RCT					
	Primary outcome: Change from baseline in HbA1c at v	veek 12				
	Secondary outcomes:					
	- Change from baseline FPG					
	- Change in total daily requirement of insulin					
	 Percentage of patients with change in HbA1c 					
	 Percentage of end patients with final HbA1c 	<7%				
Participant	N: 65 analysed					
Criteria	Inclusion criteria: Participants aged between 18 years pioglitazone (≥30mg) for ≥6 weeks and insulin therapy	and 75; type 2 diabetes, BMI \leq 45 kg/m ² , HbA1c of 7.5-10.0 (50 units) \geq 12 weeks before enrolment.	0%; taking stable dose metformin (≥1000mg) and/or			
	1. 6	g/dl (men) or <1.4 mg/dl (women), and a urine microalbur	min-to-creatinine ratio <300 mg/g or, if exceeded on			
	Exclusion criteria: Type 1 diabetes, AST and/or ALT >2 uncontrolled diabetes including a history of severe hyp	5 times the upper limits of normal, creatine kinase ≥3 time loglycemia. Any significant other disease	es the upper limits 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 plu	is insulin sensitizer and insulin as in intervention 1				
		is insulin sensitizer and insulin as in intervention 1				
	9 , 9	exercise programme (American Diabetes Associatio	n or similar local guidelines); following lead in			
		insulin could be down-titrated in patients at risk of I				
	Lead in period: 10-21 day to establish reduced in	· · · · · · · · · · · · · · · · · · ·				
Quality	Study Quality: Medium – See Quality table for further					
Participant	Group 1 (n analysed=19):	Group 2 (n= 23):	Group 3 (n= 23):			
baseline data	Placebo, OADs + insulin,	10mg dapagliflozin, OADs + insulin,	20mg dapagliflozin OD, OADs + insulin,			

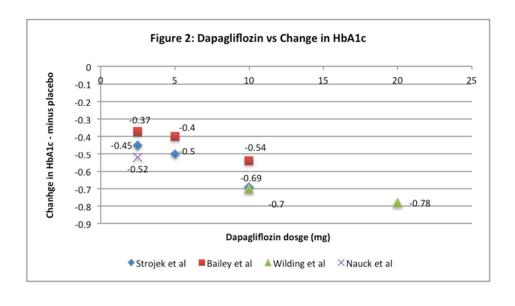
	Age (years): 58.4 SE Sex: 69.6% male		Age (years): 55.7 Sl Sex: 54.2% male		Sex: 54.2% male			
	BMI (kg/m²): 34.8 S		BMI (kg/m²): 35.5		BMI (kg/m²): 36.2			
	HbA1c (%): 8.40% S		HbA1c (%): 8.4% SE		HbA1c (%):8.5% S			
	Duration of diabete			es (years): 11.8 SD 5.8		etes (years): 11.3 SD 5.6		
	FPG (mmol/L): 9.22		FPG (mmol/L): 8.67		FPG (mmol/L): 8.			
	Systolic BP (mmHg)		Systolic BP (mmHg): n/a	Systolic BP (mmH	lg): n/a		
Outcome (change	from baseline at study		-					
	Group 1 (n analysed		Group 2 (n= 23):		Group 3 (n= 23):			
	Placebo, OADs + in:	sulin,	10mg dapagliflozin,		20mg dapagliflozi	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 hypoglycaen	nia = symptomatic episode,	General events – where frequency is >5%		At least one or more adverse event			
	capillary glucose <3.5mmol/L)		UTI = Urinary Tract Infection		Group 1 = n=15			
	Major hypoglycaemia = symptomatic episode,		GTI = Genital Tract Infection		Group 2 = n=18			
	needing external assistance with following recovery,		HypoT = Hypotension		Group 3 = n=16			
	capillary glucose <3.0mmol/l)		HypoG = Hypoglycaemia		One patient in each group discontinued due to			
					adverse effects			
Specific Events	Group 1 (n analysed	d=19):	Group 2 (n= 23):		Group 3 (n= 23):	Group 3 (n= 23):		
	Placebo, OADs + ins	sulin,	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, Hypo	G n=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 In	fection n= 2	Upper resp. Tract II	nfection n= 2	Nasopharyngitis r	1=2		
	Headache n= 2		Headache n= 3		Peripheral odema	n=2		
	Procedural pain n=2	2	Pharyngolaryngeal	pain n=2	Abdominal pain n	=2		
					Fatigue n= 1			
					Influenza n= 1			
					Pain in extremity	n= 1		
					I dill ill CALI Citility			

Safety Assessment

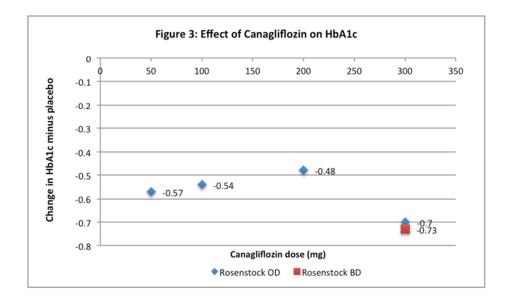




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258x143mm (72 x 72 DPI)







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

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

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ABSTRACT

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

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

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

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

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

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

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

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

INTRODUCTION

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

It is estimated that 65% of people with diabetes will die as a result of cardiovascular complications,^{2;3} therefore anti-diabetic medications need not only to produce a reduction in HbA1c, but ideally also a reduction in cardiovascular disease mortality.

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

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

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

The key questions for this review are:

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

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

METHODS

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

Eligibility criteria

Study Design

Randomised control trials (RCT) and systematic reviews of trials were used for assessing efficacy. As HbA1c is the main outcome being measured, no trial covering less than 8 weeks was accepted into the review, due to that being the minimum period required for a measureable change in HbA1c levels to be detected due to turnover of red blood cells. Quality of life (QoL) data were also sought. A change in quality of life may result from, for example, a reduction in hypoglycaemic episodes, and reduced fear of hypoglycaemia.

Participants

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

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

- Prior Medications: metformin, sulphonylureas, insulin, DPP4 inhibitors (the gliptins)
- Patients with a duration of diabetes:
 - Less than 2 years from diagnosis
 - 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 tool⁶ 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 I² statistic. Where necessary, standard deviations were calculated from confidence intervals or standard errors as described in the Cochrane Handbook. In cases where means and measures of variation were only given in graphs but not in numerical form, values were estimated from graphs.

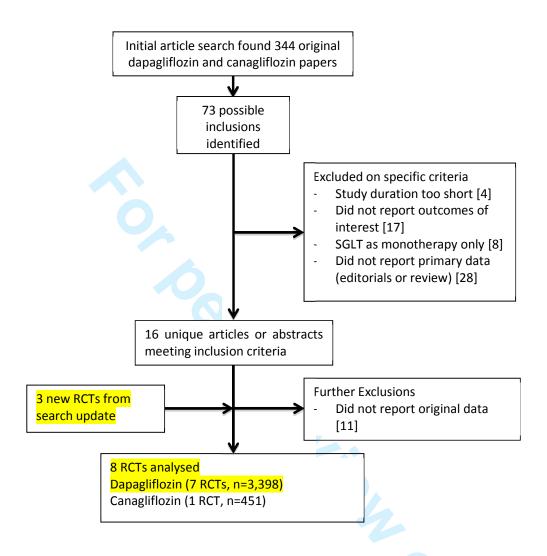
No meta-analysis using active comparators was performed due to clinical heterogeneity. Only two trials had active comparators, glipizide and sitagliptin, which have different modes of action and different effects on weight and hypoglycaemia risk.

RESULTS

Search results

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

Figure 1. Search results



Study characteristics

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

Study design

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

Study participants

Seven RCTs assessed dapagliflozin.⁸⁻¹⁵ The dapagliflozin trials included 3,398 participants. In the single canagliflozin trial, ¹⁶ 451 participants received that drug for 12 weeks.

Baseline HbA1c levels across the study populations ranged between 7.7 and 8.6% in most trials, but participants in one trial (Bolinder 2012)⁹ had baseline HbA1c levels of 7.2%.

Baseline BMI ranged between 31.2 and 36.2 kg/m², and mean age between 53 and 61 years.

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Interventions

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

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

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

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

Outcome assessment

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

Quality of included studies

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

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

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

Study design	Participants	Interventions	Outcomes
Dapagliflozin			Difference 10 mg dapagliflozin versus control (95% CI)
Bailey 2010 ⁸	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	HbA1c (%): 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/m²): 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 ^{9;10}	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	HbA1c (%): 7.2 SD0.4 to 0.5	Comparator: placebo	FPG (mmol/L): -0.95 (-1.33, -0.57)
Duration: 24 weeks	BMI (kg/m²): 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 ¹¹	N: 801	Intervention: dapagliflozin once daily	HbA1c (%): 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	HbA1c (%): 7.7 SD0.9	Comparator: glipizide (mean dose	FPG (mmol/L): -0.20 (95% CI NR)
Duration: 52 weeks	BMI (kg/m²): 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 ¹²	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	HbA1c (%): 8.3 to 8.4 SD1.0	Comparator: placebo	FPG (mmol/L): -1.33 (95% CI NR)
Duration: 24 weeks	BMI (kg/m ²): 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 ¹³	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	HbA1c (%): 8.1 SD0.7 to 0.8	Comparator: placebo	FPG (mmol/L): -1.47 (-1.86, -1.08)
Duration: 24 weeks	BMI (kg/m ²): 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 ¹⁴	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	HbA1c (%): 8.4 to 8.5 SD0.7 to 0.9	Comparator: placebo	FPG (mmol/L): -0.86 (-2.13, +0.42)
Duration: 12 weeks	BMI (kg/m²): 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 ¹⁵	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
Duration: 24 weeks	BMI (kg/m²): 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 ¹⁶	N: 451	Intervention: 50, 100, 200 or 300 mg OD	HbA1c (%): -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	BMI (kg/m²): 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:	FPG (mmol/L): -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 ⁸	Yes	Yes	Yes (double blind)	Yes – last observation carried forward	12%	Yes	Yes	Yes – 0.5% HbA1c difference detectable	Astra-Zeneca and Bristol- Myers-Squibb
Bolinder 2012 / Ljunggren 2012 ^{9;10}	Yes	Yes	Yes (double blind)	Yes – last observation carried forward	7.1%	Yes	Yes	Unclear for primary endpoint, 2% BMD difference detectable	Astra-Zeneca and Bristol- Myers-Squibb
Nauck 2011 ¹¹	Yes	Yes	Yes (double blind and double dummy)	Yes – last observation carried forward	22.1%	Yes	Yes	Yes - 0.35% HbA1c difference detectable	Astra-Zeneca and Bristol- Myers-Squibb
Rosenstock 2012 ¹²	Not reported	Not reported	Yes (double blind)	Not reported	8% at 24 weeks, 19% at 48 weeks	Yes	Unclear	Not reported	Astra-Zeneca and Bristol- Myers-Squibb
Strojek 2011 ¹³	Yes	Yes	Yes (double blind and double dummy)	Yes – last observation carried forward	8.5%	Yes	Yes	Yes – 0.5% HbA1c difference detectable	Astra-Zeneca and Bristol- Myers-Squibb
Wilding 2009 ¹⁴	Not reported	Not reported	Yes (single blind during lead in, double blind during study)	Yes – last observation carried forward	7.0%	Yes	Partially; matched for patient demographics, not for prior medications	Yes – 0.5% HbA1c difference detectable	Astra-Zeneca and Bristol- Myers-Squibb
Wilding 2012 ¹⁵	Yes	Yes	Yes (double blind and double dummy)	Yes – last observation carried forward	11% at 24 weeks, 15.5% at 48 weeks	Yes	Yes	Yes – 0.5% HbA1c difference detectable	Astra-Zeneca and Bristol- Myers-Squibb
Canagliflozin									
Rosenstock 2012 ¹⁶	Not reported	Not reported	Yes (double blind)	Yes – last observation carried forward	10.9%	Yes	Yes	Yes – 0.55% HbA1c difference detectable	Janssen Global Services

Clinical effectiveness

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

HbA1c levels

Figure 2 shows the results of the meta-analysis of 10 mg/day of dapagliflozin versus placebo for HbA1c for study durations up to 26 weeks and for 48 to 52 weeks. Figure 3 shows the reductions in HbA1c in the seven study groups of the canagliflozin study (Rosenstock 2012)¹⁶ after 12 weeks of treatment.

Dapagliflozin at a dose of 10 mg/day significantly reduced HbA1c by (WMD) -0.54% (95% CI: -0.67, -0.40, p<0.00001) after 12 to 26 weeks of treatment compared to placebo. There was significant heterogeneity, which was eliminated when excluding the only study with a baseline HbA1c <7.5% (Bolinder 2012)⁹. The WMD in HbA1c for studies with a baseline HbA1c value of >7.5% was -0.59% (95% CI: -0.67, -0.51). Change from baseline in the 10 mg dapagliflozin groups ranged between -0.39 and -0.96% (main study end), and differences to placebo between -0.29 and -0.69%. HbA1c reductions at 48 to 52 weeks were similar to those at up to 26 weeks (three studies, WMD -0.54, 95% CI: -0.69, -0.38, p<0.00001).

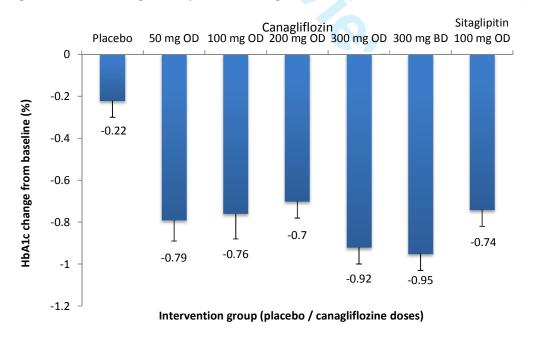
In the study by Nauck 2011,¹¹ there was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by -0.52% (95% CI: -0.60, -0.44).

Canagliflozin reduced HbA1c in a dose-related manner up to 300 mg once daily (HbA1c reductions from baseline ranging from -0.70 to 0.95%) after 12 weeks of treatment, with only a small difference between the once daily and twice daily doses at 300 mg (-0.92% SE0.08 and -0.95% SE0.08 from baseline, Figure 3). The HbA1c reduction from baseline with sitagliptin was -0.74% SE0.08.

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

	Dapaglif	lozin (10 r	ng)	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]	
Wilding 2012	-0.96	0.67	173	-0.39	0.72	166	12.5%	-0.57 [-0.72, -0.42]	<u> </u>
Subtotal (95% CI)			701			687	63.9%	-0.54 [-0.67, -0.40]	◆
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	40 50/	0.07.0.00.0.501	
			170	-0.54	0.07	100	12.5%	-0.67 [-0.82, -0.52]	
Wilding 2012	-1.01	0.72	164	-0.47	0.77	157	12.5%	-0.67 [-0.82, -0.52] -0.54 [-0.70, -0.38]	-
	-1.01							• • •	-
Subtotal (95% CI)		0.72	164 383	-0.47	0.77	157	11.7%	-0.54 [-0.70, -0.38]	*
Wilding 2012 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: 2	0.01; Chi ² = {	0.72 5.93, df = 2	164 383	-0.47	0.77	157	11.7%	-0.54 [-0.70, -0.38]	→
Subtotal (95% CI) Heterogeneity: Tau ² = 0	0.01; Chi ² = {	0.72 5.93, df = 2	164 383	-0.47	0.77	157	11.7% 36.1%	-0.54 [-0.70, -0.38]	*
Subtotal (95% CI) Heterogeneity: Tau² = 0 Test for overall effect: 2 Total (95% CI)	0.01; Chi² = 5 Z = 6.78 (P <	0.72 5.93, df = 2 0.00001)	164 383 2 (P = 0.0	-0.47 05); I ² = 66%	0.77	157 373	11.7% 36.1%	-0.54 [-0.70, -0.38] -0.54 [-0.69, -0.38]	•
Subtotal (95% CI) Heterogeneity: Tau² = 0 Test for overall effect: 2	0.01; Chi ² = { Z = 6.78 (P < 0.01; Chi ² = 2	0.72 5.93, df = 2 0.00001) 22.81, df =	164 383 2 (P = 0.0 1084 8 (P = 0	-0.47 05); I ² = 66%	0.77	157 373	11.7% 36.1%	-0.54 [-0.70, -0.38] -0.54 [-0.69, -0.38] -0.54 [-0.63, -0.44]	-1 -0.5 0 0.5 1 burs dapagliflozin Favours placeb

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

	Dapaglif	flozin (10	mg)	PI	acebo)		Mean Difference	Mean Difference	Э
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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]		
Bolinder 2012	-2.96	2.61	89	-0.88	2.62	91	8.3%	-2.08 [-2.84, -1.32]		
Rosenstock 2012	-0.14	2.3	140	1.64	2.3	139	14.8%	-1.78 [-2.32, -1.24]		
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]		
Wilding 2012 Subtotal (95% CI)	-1.61	2.51	177 713	0.43	2.51	168 701	15.2% 79.5 %	-2.04 [-2.57, -1.51] -1.81 [-2.04, -1.57]	<u>→</u>	
1.2.2 48 weeks and m	nore									
Bolinder 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]	<u>-</u>	
Wilding 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]	•	
Heterogeneity: Tau ² =	0.00; Chi ² =	0.06, df	= 2 (P =	0.97); 1	² = 0%	ı				
Test for overall effect:	Z = 9.49 (P	< 0.0000	1)							
Total (95% CI)			1100			1081	100.0%	-1.95 [-2.18, -1.71]	•	
Heterogeneity: Tau ² =	0.02; Chi ² =	9.69, df	= 8 (P =	0.29); 1	² = 17 ⁹	%			-4 -2 0	2 4
Test for overall effect:	Z = 16.17 (F	o < 0.0000	01)					F	-4 -2 U avours experimental Favour	- '
Test for subgroup diffe	erences: Chi	² = 4.33, (df = 1 (P	= 0.04), 2 = 7	76.9%		1	avours experimental i avour	3 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). ¹⁶

Fasting plasma glucose (FPG)

A significant reduction in FPG was seen in all dapagliflozin groups compared to placebo, with 10 mg dapagliflozin reducing FPG between -0.86 and -1.47 mmol/L more than control. There was no significant difference between FPG reductions with dapagliflozin versus glipizide in the study by Nauck 2011.¹¹

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

Adverse events

Urinary and genital tract infection

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

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

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

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

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

Hypoglycaemia

Overall, there was no significant difference in all types of hypoglycaemia between dapagliflozin and placebo groups. Hypoglycaemia, where data permitted, was divided into three categories: severe, moderate and other, corresponding respectively to capillary

glucose readings of; <3.0 mmol/L (with external assistance required), <3.5 mmol/L, and symptoms suggestive of hypoglycaemia, but without confirming capillary glucose measurement. The incidence of all forms hypoglycaemia in the dapagliflozin groups ranged from 1.1% (Rosenstock 2012) to 56.6%. (Wilding 2012, any dose of dapagliflozin + insulin ± OAD).

Wilding 2009, reported more than a doubling of all hypoglycaemic events when dapagliflozin and insulin were compared to placebo and insulin (27% compared to 13%), but with only 16 hypoglycaemic episodes in a total of 71 participants. ¹⁴ Strojek 2011 reported a small, dose independent, increase in hypoglycaemia from dapagliflozin 2.5 mg, 5 mg and 10 mg, producing hypoglycaemia rates of 7.1%, 7.5% and 7.9% respectively, compared to 4.7% for placebo and glimepiride, however again with only a small number hypoglycaemic events, 29 amongst 592 participants. ¹³ Nauck 2011 reported that compared to glipizide, dapagliflozin produced a significant reduction in all types of hypoglycaemic events, with an incidence of 3.4% compared to 39.7% (14 versus 162 events). ¹¹

Rosenstock 2012, comparing placebo to canagliflozin, found a hypoglycaemic event rate of 2% in the placebo group, of 0 to 6% in the canagliflozin groups (highest rate in the 200 mg once daily group, no dose dependence), and 5% in the sitagliptin group. The severity was not commented on.¹⁶

Other adverse events

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

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. ¹⁷ Nauck (2011) in one of the largest studies (801 participants), found a significantly higher incidence of hypoglycaemia in the sulphonylurea group, than with dapagliflozin. Hypoglycaemia in patients treated with SGLT2 receptor inhibitors was seen to be greatest when used in combination with insulin.

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

Implications for future practice

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

Metformin

- The sulphonylureas
- Pioglitazone
- Acarbose
- The meglitinide analogues, nateglinide and repaglinide
- The GLP-1 analogues
- The DPP-4 inhibitors
- The SGLT inhibitors
- Insulins

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

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

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

Limitations of studies reviewed

There are no long term data on SGLT2 side effects, both in terms of rare complications yet to be identified, but also on the long term effects of significant glycosuria on the urinary tract. Two extension studies, published at present only as conference abstracts, reported that weight loss was maintained to two years. Del Prato and colleagues¹⁸), 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 colleagues¹⁹) in a follow-up of 64% of original participants, reported that by two years, weight had increased by 1.8kg in the placebo group but had decreased by 1.4kg in the 10mg dapagliflozin group.

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

Data of canagliflozin come from only one paper. Only two studies (Wilding 2009 and 2012) examined use of dapagliflozin in triple therapy, with insulin, and no trials examined the role of the SGLT2 receptor inhibitors in triple oral therapy.

The costs of the drugs are not yet known so cost-effectiveness cannot be assessed. The sulphonylureas are now very low cost, so the SGLT2 receptor inhibitors are very unlikely to be cost-effective compared to them. They are likely to be used in patients in whom metformin and sulphonylureas are insufficient or not tolerated, so the main comparators may be the gliptins, which have similar effects on HbA1c, are weight-neutral and which also increase the risk of UTIs, by about 40%. ²¹

Musso et al. (2012)²¹ produced a systematic review of SGLT2 inhibitors that included 13 articles. The main reasons for the difference between our own review and that of Musso et al. is our focus on a real world use of SLGT2 inhibitors, and inclusion of recent trials. We excluded studies of less than eight weeks in duration, whilst Musso et al. analysed studies as short as two weeks. In addition, Musso et al. included studies with SGLT2 inhibitors are primary intervention, whilst the present study has only looked at SGLT2 inhibitors as in combination therapy.

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

The US Food and Drug Administration (FDA) reviewed dapagliflozin in July 2011.22 They felt unable to approve it without additional safety data, mainly because of concerns about bladder and breast cancer. In the study data, there were nine cases of breast cancer in the dapagliflozin groups and none in the control groups. Some of these cancers occurred not long after dapagliflozin had been started. The absence of breast cancers amongst the controls was considered unexpected. An analysis by the manufacturers gave a standardised incidence ratio of 1.27 (95% CI: 0.58, 2.41) but this was not sufficient to reassure the FDA

committee. There were nine cases of bladder cancer in those taking dapagliflozin and only one in the control groups, though it was noted that in five cases, haematuria had been recorded before dapagliflozin was started. The FDA committee noted that the imbalance might possibly be due to detection bias. The committee voted 9 to 6 against approval.

CONCLUSIONS

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

Contributions

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

Competing interests

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

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REFERENCES

- (1) Diabetes UK. Diabetes in the UK: Key statistics on diabetes. http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf . 2010. Accessed: 2-8-2012.
- (2) Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003; 289(1):76-79.
- (3) Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB et al. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. The MILIS Study Group. J Am Coll Cardiol 1989; 14(1):49-57.
- (4) Santer R, Kinner M, Lassen CL, Schneppenheim R, Eggert P, Bald M et al. Molecular analysis of the SGLT2 gene in patients with renal glucosuria. *J Am Soc Nephrol* 2003; 14(11):2873-2882.
- (5) Hanefeld M, Forst T. Dapagliflozin, an SGLT2 inhibitor, for diabetes. *Lancet* 2010; 375(9733):2196-2198.

- (6) Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. http://www.cochrane-handbook.org/. 2011. The Cochrane Collaboration. Accessed: 9-8-2012.
- (7) WHO. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. WHO/NCD/NCS/99.2. 1999. http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf. Accessed: 9-8-2012.
- (8) Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010; 375(9733):2223-2233.
- (9) Bolinder J, Ljunggren O, Kullberg J, Johansson L, Wilding J, Langkilde AM et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *J Clin Endocrinol Metab* 2012; 97(3):1020-1031.
- (10) Ljunggren O, Bolinder J, Johansson L, Wilding J, Langkilde AM, Sjostrom CD et al. Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. *Diabetes Obes Metab* 2012; 9999(9999).
- (11) Nauck MA, Del PS, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care* 2011; 34(9):2015-2022.
- (12) Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of Dapagliflozin, an SGLT2 Inhibitor, on HbA1c, Body Weight, and Hypoglycemia Risk in Patients With Type 2 Diabetes Inadequately Controlled on Pioglitazone Monotherapy. *Diabetes Care* 2012; 35(7):1473-1478.
- (13) Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab* 2011; 13(10):928-938.
- (14) Wilding JP, Norwood P, T'joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. *Diabetes Care* 2009; 32(9):1656-1662.
- (15) Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med* 2012; 156(6):405-415.
- (16) Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care* 2012; 35(6):1232-1238.
- (17) Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L et al. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. *Clin Pharmacol Ther* 2009; 85(5):520-526.

- (18) Del Prato S, Nauck MA, Rohwedder K, Theuerkauf A, Langkilde AM, Parikh S. Long-term efficacy and safety of dapagliflozin vs add-on glipizide in patients with type 2 diabetes inadequately controlled with metformon: 2 year results. 47th Annual Meeting of Eureopan Association for the Study of Diabetes, Lisbon September 2011; S348
- (19) Wilding JP, Woo VC, Rohwedder K, Sugg JE, Parikh SJ. Long-term effectiveness of dapagliflozin over 104 weeks in patients with type 2 diabetes poorly controlled with insulin. 72nd Scientific Session of the American Diabetes Association June 2012: A267-268
- (20) Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, Philip S. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. *Health Tech Assessment 2010;14: no 36*
 - (21) Musso G, Gambino R, Cassader M, Pagano G. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. *Ann Med* 2012; 44(4):375-393.
 - (22) Food and Drug Administration. Summary minutes of the endocronologic and metabolic drugs advisory committee. 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM262990.pdf. Accessed: 9-8-2012.

Appendix - Detailed study data

Dapagliflozin

	JL, Pieters A, Bastien A, List JF. Effect of dapagli andomised, double-blind, placebo-controlled tr		vho 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 typ	oe 2 diabetes in patients with inadequate	HbA1c control with metformin alone				
Study quality	High – see quality table for further informatio	n					
Study	Multi-centre: 80 (USA, Canada, Argentina, Me	exico, Brazil)					
particulars	Duration of intervention: 24 weeks						
	Duration of run in: 2 weeks						
	Follow-up: on completion of 24 weeks, a 102						
	Design: 4-arm parallel-group RCT, double blin						
	Primary outcome: change from baseline in HbA1c at week 24						
	Secondary outcomes:						
	At 24 weeks changes in:						
	- Fasting plasma glucose						
	- Proportion of patients achieving HbA1c <7%, number with HbA1c of 9% or more						
	- Total bodyweight, change from baseline	in bodyweight, and decreases in bodywe	eight of 5% or more				
	- Laboratory tests, adverse events						
Participant	N: 534 analysed		-1 (² · · · · · · · · · · · · · · · · · · ·				
criteria	Inclusion criteria: participants aged between	18 and // years; type 2 diabetes; BMI ≤4	15 kg/m; HbA1c / to 10.0%; fasting C-peptide	e ≥0.34 ng/ml; taking stable dose			
	metformin ≥1500 mg per day	-1/1	(i-t	University / timing time > 202 / 4 / 1			
	Exclusion criteria: serum creatinine ≥133 μmo						
	AST or ALT >three times the upper limit of normal; creatine kinase >three times the upper limit of normal, symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with >10% weight loss during the 3 months before enrolment); systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg; any						
	significant other systemic disease	during the 3 months before enrolment)	; systolic blood pressure 2180 mmng or diast	olic blood pressure 2110 mmng; any			
Interventions	Intervention 1: 2.5 mg dapagliflozin + metfori	min					
interventions	Intervention 2: 5 mg dapagliflozin + metform						
	Intervention 2: 5 mg dapagliflozin + metformin Intervention 3: 10 mg dapagliflozin + metformin						
	Intervention 3: 10 mg dapagimozin + metrorimin						
	OAD schedule: metformin at pre-study dose (≥1500 mg/day; mean dose 1792 to 1861 mg/day); dapagliflozin once daily before morning meal						
	All groups: diet and exercise counselling						
	Lead in period: 2 weeks, single blind, to assess compliance with placebo, patients randomised after successful completion; metformin dose (open label 500 mg tablets)						
	continued at pre-study levels		,,	(
Participant	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	Age: 55.0 SD9.3 years	Age: 54.3 SD9.4 years	Age: 52.7 SD9.9 years			
	Sex: 55% male	Sex: 51% male	Sex: 50% male	Sex: 57% male			

Headache n=6

			BMI (kg/m	BMI (kg/m²): 31.6 SD4.8 HbA1c (%): 7.99% SD0.90		BMI (kg/m ²): 31.4 SD5.0 HbA1c (%): 8.17% SD0.96		BMI (kg/m²): 31.2 SD5.1 HbA1c (%): 7.92% SD0.82	
			HbA1c (%)						
	Duration of diabe	etes: 5.8 SD5.1 years	Duration of	Duration of diabetes: 6.0 SD6.2 years		Duration of diabetes: 6.4 SD5.8 years		Duration of diabetes: 6.1 SD5.4 years	
	FPG (mmol/L): 9.	19 SD2.57	FPG (mmo	I/L): 8.96 SD2.39	FPG (mm	ol/L): 9.39 SD2.72	FPG (mmol/L	.): 8.66 SD2.15	
	Systolic BP (mmF	lg): 127.7 SD14.6	Systolic BF	(mmHg): 126.6 SD14.5	Systolic B	P (mmHg): 126.9 SD14.3	Systolic BP (r	nmHg): 126.0 SD15.9	
Outcome (chan	ge from baseline to	study end (week 24))							
	Group 1 (n=134):		Group 2 (n	=135):	Group 3 (n=133):	Group 4 (n=1	32):	
	Placebo OD + me	etformin	2.5 mg dap	oagliflozin 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	-0.70	-0.85 to -0.56	-0.84	-0.98 to -0.70	
				p=0.0002 vs placebo		p<0.0001 vs placebo		p<0.0001 vs placebo	
ΔWeight (kg)	-0.9	-1.4 to -0.4	-2.2	-2.7 to -1.8	-3.0	-3.5 to -2.6	-2.90	-3.3 to -2.4	
				p<0.0001 vs placebo		p<0.0001 vs placebo		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	_	aemia = symptomatic episo		· · · · · · · · · · · · · · · · · · ·		1) via patient questionnaire and vents – where frequency is		or more adverse event	
	Major hypoglyca	aemia = symptomatic episo	ode, needing e	xternal assistance with	>5%		Group 1 = n=	88	
	following recove	ry, capillary glucose <3.0m	ımol/L		UTI = Urin	ary Tract Infection	Group 2 = n=	89	
					GTI = Gen	ital Tract Infection	Group 3 = n=	95	
						HypoT = Hypotension		Group 4 = n=98	
					HypoG = H	Hypoglycaemia			
	Group 1 (n analy	/sed=134):	Group 2 (n	= 135):	Group 3 (n= 133):	Group 4 (n= 1	132):	
	Placebo OD + m	etformin	2.5 mg dap	pagliflozin OD + metformin	5 mg dapa	agliflozin OD + metformin	10 mg dapag	liflozin OD + metformin	
Specific events	UTI n=11, GTI n=	:7	UTI n= 6, G	iTI n=11	UTI n=10,	GTI n=18	UTI n=16, GT	l n=12	
	HypoT n=1, Hypo	oG n=4	HypoT n=0	, HypoG n=3	HypoT n=	2, HypoG n=5	HypoT n=0, H	ypoG n=5	
	Events leading to	o 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		Back pain		Back pain n=1		
	Nasopharyngitis	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		Influenza r	-	Influenza	-	Influenza n=8		
	Hypertension n=		Hypertens		Hypertens		Hypertension		
	Upper resp. trac	t Infection n=10	Upper resp	o. tract Infection n=5	Upper resp. tract Infection n=4		Upper resp. tract Infection n=3		

Headache n=11

Headache n=1

Headache n=4

	en Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, Sugg J, Parikh S. Effects of dapagliflozin on body weight, total fat mass, 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
•	pgy and Metabolism 2012; 97(3): 1020-1031 ⁹	Bristor Myers Squies
	(6)	SGLT2 inhibitor (10 mg dapagliflozin)
Ljunggren Ö, Bolind	der J, Johansson L, Langkilde AM, Sjöström CD, Sugg J, Parikh S. Dapagliflozin has no effect on markers of bone formation and	+ metformin
	mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes, Obesity and	versus placebo + metformin
	E-publication ahead of print] ¹⁰	
Aim: to confirm we	eight loss with dapagliflozin, and establish effect on body composition and bone metabolism in patients with type 2 diabetes with i	nadequate 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; H	
	BMI ≥25 kg/m²; weight ≤120 kg; treatment exclusively with a stable dose of metformin ≥1500 mg/day for at least 12 weeks bef	
	Exclusion criteria: men <30 years, perimenopausal women, HbA1c >8.5%, use of insulin within 6 months (except temporary ≤7	
	months; calculated creatinine clearance <60 mL/min; urine albumin:creatinine ratio >1800 mg/g (>203.4 mg/mmol); ASP and/	
	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	
Interventions	Intervention 1: 10 mg dapagliflozin + metformin	
	Intervention 2: placebo + metformin	N 1 199 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	OAD schedule: metformin at pre-study dose (≥1500 mg/day, mean dose 1901 mg SD430 in Group 1, 1989 mg SD477 in Group 2	z); dapagliflozin once daily before or with
	morning meal; in case of inadequate glycaemic control, sitagliptin 100 mg used as rescue medication	
	All groups: diet, lifestyle, exercise counselling	
	Lead in period: 2 weeks, single blind, placebo lead in	

Sec. 55% male BMI (kg/m²): 31.7 503.9 HbA1c (St): 7.16% 500.53 Duration of diabetes: 5.5 D5.3 years PFG (mmol/L): 8.3 501.4 Dutctome (change from baseline to study and £4 weeks) Group 1 (n=91): Placebo + metformin Mean S5PG (mmol/L) 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, labetests and vital signs Minor hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Minor 101 (n=91): Placebo + metformin Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Minor 101 (n=91): Placebo + metformin Minor 101 (n=91): Placebo + me	Participant	Group 1 (start n= 91,	analysed n=91): Placebo + metformin	Group 2 (start n=	Group 2 (start n= 91, analysed n= 89): 10 mg dapagliflozin + metformin			
BMI (kg/m²): 31.7 S0.3 9 HbA1c (%): 7.16% S00.63 Duration of diabetes: 5.5 S05.3 years Pr0 (mmol/L): 8.3 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.3 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.3 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.3 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.3 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.3 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.3 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.3 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of diabetes: 6.0 S04.5 years Pr0 (mmol/L): 8.2 S01.4 Duration of	baseline data	Age: 60.8 SD6.9 years	Age: 60.6 SD8.2 ye	ears				
HbALC (%): 7.19% SDD.44 Duration of diabetes: 5, 55 D.3, years								
Duration of diabetes: 5,5 SDS,3 years PFG (mmol/L): 8,3 SD1.4 PFG (mmol/L): 8,3 SD1.4 PFG (mmol/L): 8,3 SD1.4 PFG (mmol/L): 8,3 SD1.4 PFG (mmol/L): 8,2 SD1.4 PFG (mmol/L): 8,0 SD1 PFG (mmol/L): 8,0 SD1 PFG (mmol/L): 8,0 SD2 PFG (mmol/L): 9,0 SD1 PFG (mmol/L): 9,0 SD2 PFG (mmol/L): 9,0		BMI (kg/m²): 31.7 SD3	3.9	BMI (kg/m²): 32.1	SD3.9			
PFG (mmol/L): 8.3 SD1.4 District to study end (24 weeks)		HbA1c (%): 7.16% SD0	0.53	HbA1c (%): 7.19%	SD0.44			
Outcome (change from baseline to study end (24 weeks))		Duration of diabetes:	5.5 SD5.3 years	Duration of diabe	tes: 6.0 SD4.5 year	s		
Group 1 (n=91): Placebo + metformin Group 2 (n=89): 10 mg dapagliffozin + metformin		FPG (mmol/L): 8.3 SD	1.4	FPG (mmol/L): 8.2	2 SD1.4			
Mean 95% CI Mehalat (%) -0.10 -0.01 to -0.19 [from graph] -0.29 to -0.49 [from graph] , p<0.0001 vs placebo MWeight (kg) -0.88 -1.43 to -0.34 -2.96 -3.51 to -2.41, p<0.0001 vs placebo AEPG (mmol/L) +0.13 NR -0.82 NR, p<0.0001 vs placebo Mean SD Mean SD Mean SD Adverse events Assety assessment: assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits, labc tests and vital signs 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 <3.5 mmol/L Severe hypoglycaemia (HypoS) = symptomatic episode needing external assistance with appliary glucose or glucagon administration Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Group 1 (n=91): Placebo + metformin Group 2 (n=91): Placebo + metformin Group 2 (n=99): 10 mg dapagliflozin + metformin Specific events UTI n=0, GTID n=0 HypoM n=2, HypoS n=0, HypoO n=1 HypoT n=0 Events leading to discontinuation n=0 Nasopharyngitis n=5 Hyportnesion n=4 Pneumonia n=0 Angina pectoris n=0 Cystits n=1 Arthralgia n=5 Headache n=2 Diarrhoea n=0	Outcome (change	from baseline to study e	nd (24 weeks))	•				
Abhala (%) -0.10 -0.01 to -0.19 [from graph] -0.39 -0.29 to -0.49 [from graph], p<0.0001 vs placebo Abveight (kg) -0.88 -1.43 to -0.34 -2.96 -3.51 to -2.41, p<0.0001 vs placebo NR, p<0.001 vs placebo At least one of vents of v		Group 1 (n=91): Place	bo + metformin	Group 2 (n= 89): 1	.0 mg dapagliflozin	+ metformin		
AVeright (kg)		Mean	95% CI	Mean	95% CI			
AFPG (mmol/L) +0.13 NR -0.82 NR, p<0.0001 vs placebo Mean SD ASSP (mmHg) 0.1 NR -2.77 NR Adverse events Safety assessment: assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits, laboratests and vital signs Minor hypoglycaemia (HypoM) = symptomatic episode, capillary glucose c3.5mmol/L, asymptomatic episode with glucose c3.5mmol/L, asymptomatic episode needing external assistance with capillary glucose c3.0mmol/L, recovery following glucose or glucagon administration Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms, but without confirmative measurement Other hypoglycaemia (HypoO) = symptoms (HypoO) = sy	ΔHbA1c (%)	-0.10	-0.01 to -0.19 [from graph]	-0.39	-0.29 to -0.4	9 [from graph] , p<0.0001 vs p	lacebo	
Mean SD NR -2.7 NR	ΔWeight (kg)	-0.88	-1.43 to -0.34	-2.96	-3.51 to -2.4	1, p<0.0001 vs placebo		
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, laborates and vital signs Minor hypoglycaemia (HypoM) = symptomatic episode, capillary glucose 3.5mmol/L , asymptomatic episode with glucose 3.5mmol/L , severe hypoglycaemia (HypoS) = symptomatic episode needing external assistance with capillary glucose 3.5mmol/L , recovery following glucose or glucagon administration (Tie Genital Tract Infection HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (nidl) Hypo = Hypoglycaemia other HypoT = Hypotension Group 1 (n=91): Placebo + metformin Group 2 (n= 89): 10 mg dapagliflozin + metformin	ΔFPG (mmol/L)	+0.13	NR	-0.82	NR, p<0.000	1 vs placebo		
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, laboratests and vital signs 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 HypoG = Hypoglycaemia (severe) HypoM = Hypoglycaemia (severe) HypoM = Hypoglycaemia other HypoT = Hypotension No significant effect on bone formation a resorption or bone mineral density		Mean	SD	Mean	SD			
Safety assessment: assessed via adverse events from the Medical Dictionary or Regulatory Activities (MedDRA v12.1) via patient questionnaire and active questioning during visits, labotests and vital signs Minor hypoglycaemia (HypoM) = symptomatic episode, capillary glucose <3.5 mmol/L	ΔSBP (mmHg)	0.1	NR	-2.7	NR			
HypoT = Hypotension Rosignificant effect on bone formation or resorption or bone mineral density Group 1 (n=91): Placebo + metformin Group 2 (n=89): 10 mg dapagliflozin + metformin UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO n=0 HypoT n=0 Events leading to discontinuation n=0 Nasopharyngitis n=5 Hypertension n=4 Pneumonia n=0 Angina pectoris n=0 Cystitis n=1 Arthralgia n=5 Headache n=2 Diarrhoea n=0 Rosignificant effect on bone formation or resorption or bone mineral density Rosignificant effect on bone formation or resorption or bone in presorption or bone in presorption or bone in presorption or bone in presorption or bone formation or resorption or bone in presorption or bone mineral density UTI n=6, GTI n=3 HypoM n=2, HypoS n=0, HypoO n=0 HypoT n=1 Events leading to discontinuation n=5 Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=3 Angina pectoris n=0 Cystitis n=2 Arthralgia n=1 Headache n=1 Diarrhoea n=0		assistance with capilla glucagon administrati Other hypoglycaemia	ry glucose <3.0mmol/L, recovery following glucose on	e or GTI = Genital Trac HypoS = Hypoglyc HypoM = Hypogly	t Infection aemia (severe) caemia (mild)	1 death in dapagliflozin grou	p, no deaths in	
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 Pneumonia n=0 Angina pectoris n=0 Cystitis n=1 Arthralgia n=5 Headache n=2 Diarrhoea n=2 UTI n=6, GTI n=3 HypoM n=2, HypoS n=0, HypoO n=0 HypoT n=1 Events leading to discontinuation n=5 Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=0 Angina pectoris n=0 Cystitis n=1 Arthralgia n=1 Headache n=1 Diarrhoea n=0				HypoT = Hypotens	HypoT = Hypotension No sig			
HypoM n=2, HypoS n=0, HypoO n=1 HypoT n=0 Events leading to discontinuation n=0 Nasopharyngitis n=5 Hypertension n=4 Pneumonia n=0 Angina pectoris n=0 Cystitis n=1 Arthralgia n=5 Headache n=2 Diarrhoea n=2 HypoM n=2, HypoS n=0, HypoO n=0 HypoT n=1 Events leading to discontinuation n=5 Nasopharyngitis n=6 Hypertension n=4 Hypertension n=4 Pneumonia n=3 Angina pectoris n=0 Cystitis n=2 Arthralgia n=1 Headache n=1 Diarrhoea n=0		Group 1 (n=91): Place	bo + metformin	Group 2 (n= 89): 1				
Events leading to discontinuation n=0 Nasopharyngitis n=5 Hypertension n=4 Pneumonia n=0 Angina pectoris n=0 Cystitis n=1 Arthralgia n=5 Headache n=2 Diarrhoea n=2 Pissopharyngitis n=5 Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=3 Angina pectoris n=2 Cystitis n=2 Arthralgia n=1 Headache n=1 Diarrhoea n=0	Specific events	HypoM n=2, HypoS n=	e0, HypoO n=1	HypoM n=2, Hypo	HypoM n=2, HypoS n=0, HypoO n=0			
Nasopharyngitis n=5 Hypertension n=4 Pneumonia n=0 Angina pectoris n=0 Cystitis n=1 Arthralgia n=5 Headache n=2 Diarrhoea n=2 Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=3 Angina pectoris n=2 Cystitis n=2 Arthralgia n=5 Headache n=1 Diarrhoea n=0			ontinuation n=0	1				
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Cystitis n=1 Arthralgia n=5 Headache n=2 Diarrhoea n=2 Cystitis n=2 Arthralgia n=1 Headache n=1 Diarrhoea n=0		Angina pectoris n=0		Angina pectoris n				
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Diarrhoea n=2 Diarrhoea n=0		•		<u> </u>				
Nauck MA, Dei Plato 3, Meier 31, Duran-Galcia 3, Konwedder K, Eize M, Pankii 31. Dapagiilloziii versus giipizide as add-on therapy iii patients with Transitional Funding Source. Astra-zeneca a	Nauck MA, Del Pra	1 111	cia S, Rohwedder K, Elze M, Parikh SJ. Dapagliflozi i		herapy in patients	with Funding source: As	tra-Zeneca a	

type 2 diabetes wh	o have inadequate glycaemic control with metformin. Diabetes Care 201:	1; 34: 2015-2022 ¹¹ Bristol-Myers-Squibb
		SGLT2 inhibitor (up to 10 mg dapagliflozin) + metformin versus metformin + glipizide
Aim: to compare th	e efficacy, safety and tolerability of dapagliflozin with glipizide in patients	with type 2 diabetes inadequately controlled with monotherapy
Study Quality	High – see quality table for further information	
Study particulars	Multi-centre: 95 sites across 10 countries world-wide Duration of intervention: 52 weeks Duration of run in: 2 weeks Follow-up: on completion of 52 weeks, 156 week extension Design: 2-arm parallel group RCT, double-blind Primary outcome: absolute change from baseline in HbA1c at week 52 Secondary outcomes: - Change in total body weight	
	- Proportion with hypoglycaemic episode	
	 Proportion of ≥5% total weight loss 	
Participant	N: 801 analysed	
criteria	receiving stable dose metformin or metformin and one other OAD at up Exclusion criteria: creatinine clearance <60 mL/min; urine albumin: creatinine clearance clearance <60 mL/min; urine albumin: creatinine clearance	ontrolled type 2 diabetes (HbA1c >6.5 and ≤10%); BMI ≤45kg/m²; fasting C-peptide ≥0.33 nmol/ to half maximal dose for up to 8 weeks prior to enrolling; FPG ≤15 mmol/L atinine ratio >203.4 mg/mmol; AST and/or ALT and/or creatine kinase ≥3 times upper limit of ≤10 g/dL for women; abnormal TSH; systolic blood pressure ≥180 mmHg and/or diastolic blood
Interventions	to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable d All groups: diet and lifestyle advice) ment 2000 mg/day); dapagliflozin started at 2.5 mg, up-titrated to maximum tolerable dose (uplose (up to 20 mg) bilised to 1500 to 2000 mg/day; 2 weeks single blind placebo lead in prior to randomisation
Participant	Group 1 (start n= 406, analysed n=400):	Group 2 (start n= 408, analysed n= 401):
baseline data	9.2 mg dapagliflozin + metformin	16.4 mg glipizide + metformin
	Age: 58 SD9 years Sex: 55.3% male BMI (kg/m²): 31.7 SD5.1 ≥ 25 kg/m²: 95% ≥ 30 kg/m²: 57%	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%

	Group 1 (n=400): 9.2 mg dapagliflozin + met	formin	Group 2 (n= 401): 16.4 mg glipizide + metformin			
	Mean 95	95% CI	Mean	95% CI		
ΔHbA1c (%)	-0.52 -0	0.60 to -0.44	-0.52	-0.60 to -0.44, NS		
ΔWeight (kg)	-3.22 -3	3.56 to -2.87	+1.44	+1.09 to +1.78, p<0.0001		
ΔFPG (mmol/L)	-1.24 -1	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	t: assessed via adverse events from the Medical	Dictionary or Regulatory Activities	(MedDRA v12.1) via patient questionnaire ar	nd active questioning during visits		
	Severe hypoglycaemia (HypoS) = symptomatic assistance with following recovery, capillary Minor hypoglycaemia (HypoM) = symptomatic <3.5mmol/L Other hypoglycaemia (HypoO) = symptoms, confirming	glucose <3.0mmol/L atic episode, capillary glucose	General events – where frequency is ≥3% UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe) HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia other HypoT = Hypotension	At least one or more adverse event Group 1 = n=318 Group 2 = n=318 No deaths in dapagliflozin group 3 deaths in glipizide group		
	Group 1 (n=406): 9.2 mg dapagliflozin + met	formin	Group 2 (n= 408): 16.4 mg glipizide + me	Group 2 (n= 408): 16.4 mg glipizide + metformin		
Specific events	UTI n=44, GTI n=50 HypoS n=0, HypoM n=7, HypoO n=7 HypoT n=6 Renal impairment / failure n=24 Events leading to discontinuation n=37 (0 du	ue to hypoglycaemia)	UTI n=26, GTI n=11 HypoS n=3, HypoM n=147, HypoO n=40 HypoT n=3 Renal impairment / failure n=14 Events leading to discontinuation n=24 (6 due to hypoglycaemia)			
	Diarrhoea n=19 Nausea n=14 Vulvovaginal mycotic infection n=14 Back pain n=19 Nasopharyngitis n= 43 Cough n=15 Influenza n=30 Arthralgia n=11 Upper resp. tract Infection n=24	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	Diarrhoea n=26 Nausea n=15 Vulvovaginal mycotic infection n=2 Back pain n=20 Nasopharyngitis n=61 Cough n=20 Influenza n=30 Arthralgia n=21			
	Headache n=21 Hypertension n=30		Upper resp. tract Infection n=31 Headache n=17 Hypertension n=35			

		n SGLT2 inhibitor, on HbA1c, body weight, and hypoglycaemia monotherapy. Diabetes Care 2012; 35: 1473-1478 ¹²	Funding source: Astra-Zeneca and Bristol-Myers-Squibb				
			SGLT2 inhibitor (5 or 10 mg dapagliflozin) + pioglitazone versus placebo + pioglitazone				
Aim: to examine the	e safety and efficacy of dapagliflozin added to piogli	tazone in type 2 diabetes patients inadequately controlled on p	ioglitazone				
Study quality	Low – see quality table for further information						
Study particulars	Multi-centre: 105 (Argentina, Canada, India, Mex	ico, 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, p						
	Primary outcome: change from baseline in HbA1c at week 24						
	Secondary outcomes:						
	At week 24, change from baseline in:						
	- Fasting plasma glucose						
	- Postprandial glucose						
	- Total body weight						
	- Blood pressure						
	 Adverse events, laboratory values, vital signs 						
Participant	N: 420 analysed	es; age ≥18 years; fasting C-peptide ≥1.0 ng/mL; BMI ≤45 kg/m²					
criteria	and HbA1c ≥7.0 to ≤10.5%; Group B: drug naïve for with hbA1c ≥8.0 and ≤11.0% or had received ≥8 w oral antidiabetic medication; Group B underwent increased to 45 mg/day if possible; pre-randomissions.	or previous 10 weeks with HbA1c \geq 8.0 to \leq 11.0% or had receive veeks of metformin \leq 1700 mg/day or sulphonylurea \leq half maxir 10 week dose optimisation in which initial therapy was discontation HbA1c had to be \geq 7.0 and \leq 10.5% mit of normal; total bilirubin $>$ 2.0 mg/dL, serum creatinine \geq 2.0	d 15 mg/day pioglitazone or any dose of rosiglitazone mal dose with HbA1c ≥7.0 to ≤11.0%, not more than or inued and pioglitazone 30 mg/day was started and				
Interventions		eng/day; dapagliflozin once daily; in case of inadequate glycaemi cients were eligible for open label rescue medication (metformin					
	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 + pioglitazon				
baseline data	Age: 53.5 SD11.4 years	Age: 53.2 SD10.9 years	Age: 53.8 SD10.2 years				
	Sex: 51.1% male	Sex: 55.3% male	Sex: 42.1% male				
	BMI: 61.2% ≥30 kg/m ² ; 87.8% ≥25 kg/m ²	BMI: $61.7\% \ge 30 \text{ kg/m}^2$; $86.5\% \ge 25 \text{ kg/m}^2$	BMI: $51.4\% \ge 30 \text{ kg/m}^2$; $92.9\% \ge 25 \text{ kg/m}^2$				
	HbA1c: 8.34% SD1.00	HbA1c: 8.40% SD1.03	HbA1c: 8.37% SD0.96				
	Duration of diabetes: 5.07 SD5.05 years	Duration of diabetes: 5.64 SD5.36 years	Duration of diabetes: 5.75 SD6.44 years				

	FPG (mmol/L): 8.92 SD2	.61	FPG (mmol/L): 9.36 SD	2.89	FPG (mmol/L): 9.15 SD2.57		
Outcome (change	from baseline to study end)					
	Group 1 (n=139): Placeb	o + pioglitazone	Group 2 (n=141): 5 mg	dapagliflozin + pioglitazone	Gro	up 2 (n=140):	10 mg dapagliflozin + pioglitazone
	Mean	SE	Mean		Mea	ın	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	4	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							
Safety assessment	t: assessed at every visit, qu	estioning, laboratory tests	and vital signs				
		HypoM) = symptomatic epi	•	General events – where		At least one	e or more adverse event
		atic episode with glucose <		6 mmol/L frequency is >5% de needing external UTI = Urinary Tract Infection		Group 1 = 6	66.9%
	Severe hypoglycaemia (HypoS) = symptomatic epis	sode needing external			Group 2 = 6	
		glucose <3.0mmol/L, recov				Group 3 = 7	0.7%
	glucagon administration			HypoS = Hypoglycaemia (sever		-	
	Other hypoglycaemia (H	lypoO) = symptoms, but wi	thout confirmative	it confirmative HypoM = Hypoglycaemia (mild)			
	measurement			HypoO = Hypoglycaemia othe			
	Group 1 (n=139): Placeb	o + pioglitazone	Group 2 (n=141): 5 mg	Group 2 (n=141): 5 mg dapagliflozin + pioglitazone		Group 2 (n=140): 10 mg dapagliflozin + pioglitazo	
Specific events	UTI n=11, GTI n=4		UTI n=12, GTI n=13		UTI n=7. GTI n=12		2
•	Any hypoglycaemia n=1,	HypoS n=0	Any hypoglycaemia n=3	Any hypoglycaemia n=3, HypoS n=0		Any hypoglycaemia n=0, HypoS n=0	
	Decreased renal function	n n=1	Decreased renal function	Decreased renal function n=2		Decreased renal function n=2	
	Events leading to discon	tinuation 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		16
	Nasopharyngitis n=7		Nasopharyngitis n=7		Nasopharyngitis n=11		
	Diarrhoea n=6		Diarrhoea n=5	Diarrhoea n=5		Diarrhoea n=9	
	Back pain n=4		Back pain n=5		Back	c pain n=8	
	Upper resp. tract infection	on n=10	Upper resp. tract infect	ion n=10	Upper resp. tract infection n=7		infection n=7
	Headache n=10		Headache n=3		Headache n=4		
	Pain in extremity n=1		Pain in extremity n=10		Pain in extremity n=4		
	Oedema peripheral n=9		Oedema peripheral n=6	5	Oedema peripheral n=3		

		 Effect of Dapagliflozin in patients with typ blind, placebo-controlled trial. Diabetes, Obe 						
				SGLT2 Inhibitor (2.5, 5, or 10 mg dapagliflozin) plus glimepiride versus placebo plus glimepiride				
	The state of the s	pagliflozin treatment, as an add-on therapy t	o glimepiride, in patients with inadequately o	controlled type 2 diabetes who had bee				
treated with sul	phonylurea monotherapy							
Study quality	High – see quality table for further inforr							
Study	Multi-centre: 84 sites across 7 countries	world-wide						
particulars	Duration of intervention : 24 weeks							
	Duration of run in : 1 week for patients s							
	Follow-up: on completion of 24 weeks, 2							
	Design: 4-arm parallel group RCT, double							
	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		2 di-h (11h-44 - > 7 h- <40 00(), DA41 <451	/ ² t- - -				
criteria	, , , , , , , , , , , , , , , , , , , ,	ears and older; inadequately controlled type		m; on stable sulphonylurea dose (at				
		at least 8 weeks prior to enrolment); fasting		mal: 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		egnancy of factation, use of weight loss med	ication within 30 days					
interventions	Intervention 1: placebo + glimepiride Intervention 2: 2.5 mg/day dapagliflozin + glimepiride							
	Intervention 2: 2.5 mg/day dapagliflozin + glimepiride Intervention 3: 5 mg/day dapagliflozin + glimepiride							
	Intervention 3: 5 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 activit							
	Lead in period: 1 week for inclusion/exclusion review for those switched to 4 mg/day glimepiride							
			Group 3 (n= 145)	Group 4 (n= 151)				
Participant Participant	Group 1 (n= 146)	Group 2 (n= 154)	GIOUD 3 (II- 143)	010up 4 (11- 131)				
•	Group 1 (n= 146)	Group 2 (n= 154) 2.5 mg dapagliflozin + glimepiride	• •					
•		Group 2 (n= 154) 2.5 mg dapagliflozin + glimepiride Age: 59.9 SD10.14 years	5 mg dapagliflozin + glimepiride Age: 60.2 SD 9.73 years	10 mg dapagliflozin + glimepiride				
Participant baseline data	Group 1 (n= 146) Placebo + glimepiride	2.5 mg dapagliflozin + glimepiride	5 mg dapagliflozin + glimepiride					

	kg/m²		HbA1c: 8.11% SD0.75		HbA1c: 8.12% SD0.78		HbA1c: 8.07% SD0.79		
	HbA1c: 8.15% SD0.74		Duration of diabetes: 7.7 SD6.0 years		Duration of diabetes: 7.4 SD5.7 years		Duration of diabetes: 7.2 SD5.5 years		
	Duration of	diabetes: 7.4 SD5.7 years	FPG (mmol/L): 9.56 SD2.13		FPG (mmol	I/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 B	P (mmHg): 132.4	
	Systolic BP	(mmHg): 133.3							
Outcome (chan	ge from baseli	ne to study end (week 24))							
	Group 1 (n=	: 146)	Group 2 (n	= 154)	Group 3 (n	= 145)	Group 4 (n= 151)	
	Placebo + gl	imepiride	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		-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 ≥3% in any group UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia	At least one or more adverse event Group 1 = n=69; Group 2 = n=80 Group 3 = n=70; Group 4 = n=76 1 death in dapagliflozin 2.5 mg 1 death in dapagliflozin 10 mg	
	Group 1 (n= 146)	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	pod P, T'joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of sensitizers. Applicability of a novel insulin-independent treatment. Diabetes Care 2009; 32(9): 1656-1662 ¹⁴ 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): 10 m	ng dapagliflozin + OAD + insulin	Group 3 (n= 24): 20 mg dapagliflozin + OAD + insulin			
baseline data	Age: 58.4 SD6.5 years		Age: 55.7 SD9.2 years		Age: 56.1 SD10.6 years			
	Sex: 69.6% male		Sex: 54.2% male		Sex: 54.2% male	Sex: 54.2% male		
	BMI (kg/m²): 34.8 SD4.6		BMI (kg/m ²): 35.5 SD	3.6	BMI (kg/m ²): 36.2	SD4.6		
	HbA1c: 8.40% SD0.9		HbA1c: 8.4% SD0.7		HbA1c: 8.5% SD0.			
	Duration of diabetes: 13	3.8 SD 7.3 years	Duration of diabetes:	: 11.8 SD5.8 years		tes: 11.3 SD5.6 years		
	FPG (mmol/L): 9.22 SD 2	•	FPG (mmol/L): 8.67 S		FPG (mmol/L): 8.9	•		
	Systolic BP (mmHg): NR		Systolic BP (mmHg):		Systolic BP (mmH			
Outcome (change	from baseline at study end				(67		
	Group 1 (n=23): Placebo		Group 2 (n= 24): 10 m	ng 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		
Safety assessmen	t: treatment-emergent adve Minor hypoglycaemia =	rse events, vital signs, laborato symptomatic episode,	General events – who	ere frequency is >5%	At least one or me	ore adverse event		
•	Minor hypoglycaemia =	symptomatic episode,	General events – who	ere frequency is >5%	At least one or mo	ore adverse event		
	capillary glucose <3.5mr	nol/L	UTI = Urinary Tract In	fection	Group 1 = n=15 Group 2 = n=18 Group 3 = n=16			
	Major hypoglycaemia =	symptomatic episode,	GTI = Genital Tract Inf	fection				
	needing external assista	nce with following recovery,	HypoT = Hypotension	, HypoG = Hypoglycaemia				
	capillary glucose <3.0mr	nol/L	HypoS = major hypog					
	Group 1 (n=23): Placebo	+ OAD + insulin	Group 2 (n= 24): 10 m	ng dapagliflozin + OAD + insulin	Group 3 (n= 24): 20 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 r	n=7, HypoS n=0	HypoT n=NR, Hypo	oG n=6, HypoS n=0		
	Events leading to discon	tinuation n=1	Events leading to disc	continuation 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=2		Vulvovaginal myco	otic infection n=3		
Upper abdominal pain n= 2			Fatigue n=2		Anxiety n=2			
	Upper abdominal pain n	= 2			Back pain n=2			
	Influenza n=2	= 2	Influenza n=1		Back pain n=2			
		= 2	- C		Back pain n=2 Dry Mouth n=2			
	Influenza n=2		Influenza n=1			=2		
	Influenza n=2 Pain in extremity n=1		Influenza n=1 Pain in extremity n=2		Dry Mouth n=2			
	Influenza n=2 Pain in extremity n=1 Upper resp. tract Infecti		Influenza n=1 Pain in extremity n=2 Upper resp. tract Infe	ection n=2	Dry Mouth n=2 Nasopharyngitis n	a n=2		
	Influenza n=2 Pain in extremity n=1 Upper resp. tract Infecti Headache n= 2		Influenza n=1 Pain in extremity n=2 Upper resp. tract Infe Headache n=3	ection n=2	Dry Mouth n=2 Nasopharyngitis n Peripheral oedem	a n=2		
	Influenza n=2 Pain in extremity n=1 Upper resp. tract Infecti Headache n= 2		Influenza n=1 Pain in extremity n=2 Upper resp. tract Infe Headache n=3	ection n=2	Dry Mouth n=2 Nasopharyngitis n Peripheral oedem Upper abdominal	a n=2		

				p. tract Infection n=1						
	oo V, Soler NG, Pahor A, Sugg J, Rohwedder doses of insulin. A randomized trial. Annals			Bristol-Myers-Squibb SGLT2 Inhibitor (2.5, 5 or 10 mg						
				dapagliflozin) + insulin ± OAD						
Aimer to ovaluat	to the officery and cafety of adding damaglifly	orin to nationts whose type 2 diabetes is ina	doguataly controlled with insulin with or w	versus placebo + insulin ± OAD						
	te the efficacy and safety of adding dapagliflo	•	dequately controlled with insulin with or w	ithout oral antidiabetic drugs						
Study quality Study	High – see quality table for further inform Multi-centre: 126 worldwide	ation								
oarticulars	Duration of intervention: 24 weeks									
particulars	Duration of intervention: 24 weeks Duration of run in: 2 week enrolment									
		ali autonolan plua funthan FCali auton	alan in muanuan							
	Design: 4-arm parallel group RCT, double	week extension plus further 56 week exter	ision in progress							
	Primary outcome: change from baseline in									
	Secondary outcomes:	I HDATC to week 24								
	- Change in total body weight									
	- Change in total body weight - Change in calculated mean daily insulin dose									
	- Change in Calculated mean daily insulin dose - Proportion with mean daily insulin reductions of ≥10% from baseline									
	- Change in FPG	ddetions of 210% from baseline								
	- Laboratory tests, adverse events, vita	al signs								
Participant	N: 800 analysed	ar signs								
criteria		een 18 and 80 years; type 2 diabetes; BMI ≤4	15 kg/m ² · inadequate glycaemic control (Hh	A1c >7 5 to <10 5%): stable insulin regime						
criteria		ks; additional treatment with up to two OAL								
	dose of other OADS for ≥8 weeks)	ks, additional treatment with up to two OAL	allowed (£1500 mg metrorimin or maxima	an tolerated dose of at least han maximal						
		f poorly controlled diabetes; calculated crea	atinine clearance <50 ml/min ner 1 73 m ² or	serum creatinine >177 umol/L or if						
	receiving metformin >133 µmol/L for men		atiline clearance 130 mily mili per 1.73 m ol	Serum ereatimine ±177 μmoly £, or m						
Interventions	Intervention 1: placebo + insulin ± OAD	Tot 2124 pinory 2 for Women								
interventions	Intervention 2: 2.5 mg dapagliflozin + insu	ılin + OAD								
	Intervention 3: 5 mg dapagliflozin + insuli									
	Intervention 3: 5 mg dapagliflozin + insulin ± OAD Intervention 4: 10 mg dapagliflozin + insulin ± OAD									
	OAD/insulin schedule: dapagliflozin once daily; open label treatment with usual daily dose of insulin (mean daily dose 77.1 U) and existing OADs (none in ~50%, metformin									
	only in ~40%, metformin in combination in ~5 to 8%, other OAD / combination in ~1.5 to 6%); OAD doses could be decreased when hypoglycaemia was a concern; insulin									
	could be up-or down-titrated if needed	1 5 to 676, other GAB / combination in 1.5	to only, one doses could be decreased with	en nypogrycucimu was a concern, msaim						
	•	and exercise regimen; Lead in period: uncl	ear							
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						
Jasemie auta	Age: 58.8 SD8.6 years	Age: 59.8 SD7.6 years	Age: 59.3 SD7.9 years	Age: 59.3 SD8.8 years						
	Sex: 49.2% male	Sex: 49.5% male	Sex: 47.4% male	Sex: 44.8% male						
	BMI (kg/m ²): 33.1 SD5.9	BMI (kg/m²): 33.0 SD5.0	BMI (kg/m²): 33.0 SD5.3	BMI (kg/m²): 33.4 SD5.1						
	HbA1c (%): 8.47% SD0.77	HbA1c (%): 8.46% SD0.78	HbA1c (%): 8.62% SD0.89	HbA1c (%): 8.57% SD0.82						
	Duration of diabetes: 13.5 SD7.3 years	Duration of diabetes: 13.6 SD6.6 years	Duration of diabetes: 13.1 SD7.8 years	Duration of diabetes: 14.2 SD7.3 years						
	FPG (mmol/L): 9.5 SD3.2	FPG (mmol/L): 10.0 SD3.3	FPG (mmol/L): 10.3 SD3.3	FPG (mmol/L): 9.6 SD3.0						
	11 3 (mm 0)/ L J. 3.3 3D3.2	11 G (mm ol/ E). 10.0 303.3	11 G (IIIII IOI) EJ. 10.3 303.3	11 3 (minor) Ej. 3.0 303.0						

	Systolic BP (mr	nHg): 136.1 SD17.2	Systolic BP (mmHg): 139.6 SD17.7	Systolic B	P (mmHg): 137.8 SD16.2	Systolic BP (mmHg): 140.6 SD16.7			
Outcome (chan	ge from baseline	to study end)								
	Group 1 (n ana	lysed=193):	Group 2 (n=202):		Group 3 (r	n=211):	Group 4 (n=194):			
	Placebo + insulin ± OAD		2.5 mg dapagliflozin + insulin ± OAD		5 mg dapa	ngliflozin + insulin ± OAD	10 mg dapagliflozin + 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 placebo		
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 placebo		
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 placebo		
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 NR		
Adverse events										
Safety assessme	ent: adverse ever	nts, laboratory values, vital	signs							
		ycaemia = symptomatic epi			General e	vents – where frequency is	At least one	or more adverse event		
	Major hypogly	ycaemia = symptomatic epi	sode, needing	external assistance with	≥5%		Group 1 = n=	Group 1 = n=144		
		very, capillary glucose <3.0			UTI = Urin	ary Tract Infection	Group 2 = n=153 Group 3 = n=153			
	Other hypogly	/caemia = suggestive criteri	a not meeting	criteria for major or minor	GTI = Gen	ital Tract Infection				
	hypoglycaemia	a			HypoT = H	lypotension	Group 4 = n=	Group 4 = n=145		
						ypoglycaemia (severe)				
						Hypoglycaemia (mild)	2 deaths in th	ne 5 mg dapagliflozin group		
			•			Hypoglycaemia (other)				
	Group 1 (n an	•	Group 2 (n=202):		Group 3 (r	•	Group 4 (n=194):			
	Placebo + insu		2.5 mg dapagliflozin + insulin ± OAD			ngliflozin + insulin ± OAD	10 mg dapagliflozin + insulin ± OAD			
Specific events	UTI n=10, GTI	n=5	UTI n=16, G	ΓI n=13	UTI n=23,	GTI n=21	UTI n=20, GTI n=21			
	HypoT n=2		HypoT n=5		HypoT n=5		HypoT n=3			
		/poM n=99, HypoO n=11		HypoM n=118, HypoO n=19		2, HypoM n=113, HypoO n=24	HypoS n=3, HypoM n=99, HypoO n=21			
		nent / failure n=3		rment / failure n=2		airment / failure n=6	Renal impairment / failure n=4			
		to discontinuation n=3		ng to discontinuation n=2		ding to discontinuation n=5		g to discontinuation n=5		
	Nasopharyngit		Nasopharyn	•		yngitis n=35	Nasopharyng			
	Headache n=1		Headache n		Headache		Headache n=			
	Back pain n=1		Back pain n=		Back pain		Back pain n=:			
	Hypertension		Hypertensio		Hypertens		Hypertension			
	Diarrhoea n=8		Diarrhoea n		Diarrhoea		Diarrhoea n=			
		n=3Peripheral oedema	Constipation		Constipati		Constipation			
	n=15		Peripheral o			l oedema n=5	Peripheral oe			
		act Infection n=12		tract Infection n=6		p. tract Infection n=8		ract Infection n=9		
	Arthralgia n=1	1	Arthralgia n	=4	Arthralgia	n=3	Arthralgia n=7			



Canagliflozin

	ggarwal N, Polidori D, Zhao` inhibitor, as add-on to me					ose Fun	ding source: Janssen	Global Services				
						or 3 vers vers	.T2 Inhibitor (50, 100 800 mg BD canaglifloz sus sitaglipitin + meti sus placebo + metfor	in) + metformin ormin				
	he safety, tolerability and e			e 2 diabetes who have	e inadequate glycaem	nic control on metform	min monotherapy					
Study quality	Medium – see quality ta		mation									
Study	Multi-centre: 85 (12 cou											
particulars	Duration of intervention											
	Duration of run in : 4 we											
	Follow-up: 2 weeks post	:-treatment										
	Design: 7-arm parallel gr	roup RCT, double bl	ind, placebo controlled	t								
	Primary outcome: chang	ge from baseline in	HbA1c to week 12									
	Secondary outcomes:											
	 Change in FPG 											
	 Change in weight 											
	- Overnight glucose-to-creatinine ratio											
	- Change in proportion	on of participants w	ith HbAc <7.0% and <6	5.5%								
	 Loss of beta cell fur 	nction measured usi	ng HOMA2-%B									
	- Serum lipids											
	 Adverse events, lab 	oratory assessment	ts, vital signs									
Participant	N: 451 analysed											
criteria	Inclusion criteria: partic							e (≥3 months) dose				
	of ≥1500 mg/day; stable	body weight; BMI	25 (24 for Asians) to 45	5 kg/m²; serum creatir	nine <1.5mg/dl for me	en and <1.4mg/dl for	women					
	Exclusion criteria: not sp	pecifically reported										
Interventions	Intervention 1: placebo	(pla) + metformin										
	Intervention 2: canaglif											
	Intervention 3: canaglif	-										
	Intervention 4: canagliflozin 200 mg OD + metformin											
	Intervention 5: canaglifle	ozin $300 \text{ mg } \Omega D + m$	netformin									
	Intervention 6: canaglifle											
	Intervention 6: canaglifl Intervention 7: sitaglipti	ozin 300 mg BD + m n (sita) 100 mg OD	etformin + metformin									
	Intervention 6: canaglif	ozin 300 mg BD + m n (sita) 100 mg OD	etformin + metformin									
	Intervention 6: canaglifl Intervention 7: sitaglipti	ozin 300 mg BD + m n (sita) 100 mg OD iin mean dose 1890 tment screening ph	etformin + metformin SD479 mg/day ase									
Participant	Intervention 6: canaglifl Intervention 7: sitaglipti OAD schedule: metform	ozin 300 mg BD + m n (sita) 100 mg OD iin mean dose 1890	etformin + metformin SD479 mg/day	Group 3 cana	Group 4 cana	Group 5 cana	Group 6 cana	Group 7 sita				
•	Intervention 6: canaglifl Intervention 7: sitaglipti OAD schedule: metform	ozin 300 mg BD + m n (sita) 100 mg OD iin mean dose 1890 tment screening ph	etformin + metformin SD479 mg/day ase Group 2 cana 50 mg OD + met	100 mg OD + met	200 mg OD + met	300 mg OD + met	300 mg BD + met	100 mg OD + met				
Participant baseline data	Intervention 6: canaglifl Intervention 7: sitaglipti OAD schedule: metform Lead in period: pre-trea	ozin 300 mg BD + m in (sita) 100 mg OD in mean dose 1890 tment screening ph Group 1 pla + met (n=65)	etformin + metformin SD479 mg/day ase Group 2 cana 50 mg OD + met (n=64)	100 mg OD + met (n=64)	200 mg OD + met (n=65)	300 mg OD + met (n=64)	300 mg BD + met (n=64)	100 mg OD + met (n=65)				
•	Intervention 6: canaglifl Intervention 7: sitaglipti OAD schedule: metform	ozin 300 mg BD + m n (sita) 100 mg OD in mean dose 1890 tment screening ph Group 1 pla +	etformin + metformin SD479 mg/day ase Group 2 cana 50 mg OD + met	100 mg OD + met	200 mg OD + met	300 mg OD + met	300 mg BD + met	100 mg OD + met				

	BMI (kg/m ²)	30.6 SD4.6	31.7	SD4.6	31.7 SD	5.0	31.4 SD5.2		31.6 SD4.9		31.8 SD5.2	31.6 SD5.0	
	HbA1c (%)	7.75 SD0.83	8.00	SD0.99	D0.99 7.83 SD0.96		7.61 SD0.8	0	7.69 SD1.0	2	7.73 SD0.89	7.64 SD0.95	
	Diab. duration (yea	ers) 6.4 SD5.0	5.6 9	D5.0	6.1 SD4.7		6.4 SD5.7 5.		5.9 SD5.2		5.8 SD4.6	5.6 SD4.7	
	FPG (mmol/L)	9.1 SD2.1	9.4 9	D2.5	9.3 SD2	.3	8.9 SD2.1		8.8 SD2.4		8.7 SD1.9	8.8 SD2.3	
	SBP (mmHg)	125 SD10	127	SD11	127 SD1	13 124 SD11			126 SD12		128 SD13	129 SD13	
Outcome (chang	e from baseline at st	udy end (12 weeks))	•					•			•		
, ,	Group 1 pla + met	Group 2 cana 50	0 mg OD	Group 3	3 cana	Group 4	cana	Group 5	cana	Gr	oup 6 cana	Group 7 sita 100 mg	
	(n=65)	+ met (n=64)	Ū	100 mg	OD + met	200 mg	OD + met	300 mg	OD + met	30	0 mg BD + met	OD + met (n=65)	
	, ,	, ,		(n=64)		(n=65)		(n=64)		(n=	=64)	, ,	
ΔHbA1c (%) [SE	-0.22 SE0.08	-0.79 SE0.1			0.12	-0.70 SE	0.08	-0.92 SE	0.08	-0.	95 SE0.08	-0.74 SE0.08	
from graph]		p<0.001 vs place	ebo	p<0.001	L vs placebo	p<0.001	vs placebo		vs placebo	p<	0.001 vs placebo	p<0.001 vs placebo	
ΔWeight (kg)	-1.1 SE0.29	-2.3 SE0.39		-2.6 SEC	•	-2.7 SEC	•	-3.4 SE0			4 SE0.29	-0.6 SE0.39	
[SE from graph]		p<0.001 vs place	ebo		L vs placebo		vs placebo		vs placebo		0.001 vs placebo	NS vs placebo	
ΔFPG (mmol/L)	+0.2 SE0.20	-0.9 SE0.22		-1.4 SEC		-1.5 SEC		-1.4 SEO			3 SE0.20	-0.7 SE0.20	
[SE from graph]		p<0.001 vs place			L vs placebo		vs placebo		vs placebo		0.001 vs placebo	p NR	
ΔSBP (mmHg)	-1.3 SE1.5	-0.9 SE1.7, p NR		_	1.3, p NR	•	.8, p NR		.5, p NR		6 SE1.4, p NR	-0.8 SE1.4, p NR	
Adverse events	· I	, , , , , , , , , , , , , , , , , , ,		Y		ı	- 1	1		ı .	, i		
	nt: adverse event rep	orts (Medical Dictiona	ry for Reg	ulatory Ac	tivities), vital si	igns, physi	cal examinatio	ns. labora	tory assess	ments.	self-administered var	ginal swabs	
		ia (HypoM) = sympton			neral events –						or more adverse ev		
	capillary glucose <3.5				UTI = Urinary Tract Infection					p 1 = n=			
		i ia (HypoS) = symptom	natic episo							Group 2 = n=32 Group 3 = n=30 Group 4 = n=26			
		istance with following		·									
	capillary glucose <3.0		,,										
		a (HypoO) = symptom	s, but	'				Group !		-			
	without measuremen		,						Grou	Group 6 = n=36			
		· ·								p 7 = n=			
		Group 1 pla (n=65)	Group 2	cana	Group 3 ca	na	Group 4 cana	G	roup 5 can	•	Group 6 cana	Group 7 sita	
			50 mg O		100 mg OD		200 mg OD (n		00 mg OD (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		=2		n=4	n=1	
	Symptomatic Hypo	n=1	n=0		n=1		n=4		=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		=2		n=2	n=0	
	discontinuation												
	Headache	n=2	n=1		n=5	İ	n=2	n	=3		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		- =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



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,^{2;3} therefore anti-diabetic medications need not only to produce a reduction in HbA1c, but ideally also a reduction in cardiovascular disease mortality.

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

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

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

The key questions for this review are:

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

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

METHODS

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

Eligibility criteria

Study Design

Randomised control trials (RCT) and systematic reviews of trials were used for assessing efficacy. As HbA1c is the main outcome being measured, no trial covering less than 8 weeks was accepted into the review, due to that being the minimum period required for a measureable change in HbA1c levels to be detected due to turnover of red blood cells. Quality of life (QoL) data were also sought. A change in quality of life may result from, for example, a reduction in hypoglycaemic episodes, and reduced fear of hypoglycaemia.

Participants

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

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

- Prior Medications: metformin, sulphonylureas, insulin, DPP4 inhibitors (the gliptins)
- Patients with a duration of diabetes:
 - Less than 2 years from diagnosis
 - 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 tool⁶ 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

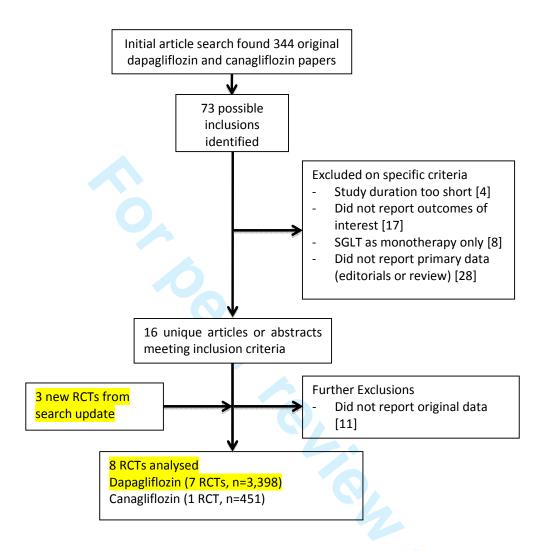
The data analysis has been reported according to the guide set down within the Cochrane Handbook for Systematic Reviews of Interventions. Meta-analysis was carried out for comparing HbA1c and weight results for 10 mg dapagliflozin versus placebo in the intermediate term (12 to 26 weeks) and longer term (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 I² 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.



Study characteristics

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

Study design

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

Study participants

Seven RCTs assessed dapagliflozin.⁸⁻¹⁵ The dapagliflozin trials included 3,398 participants. In the single canagliflozin trial, ¹⁶ 451 participants received that drug for 12 weeks.

Baseline HbA1c levels across the study populations ranged between 7.7 and 8.6% in most trials, but participants in one trial (Bolinder 2012)⁹ had baseline HbA1c levels of 7.2%.

Baseline BMI ranged between 31.2 and 36.2 kg/m², and mean age between 53 and 61 years.

Interventions

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

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

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

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

Outcome assessment

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

Quality of included studies

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

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

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

Study design	Participants	Interventions	Outcomes
Dapagliflozin			Difference 10 mg dapagliflozin versus control (95% CI)
Bailey 2010 ⁸	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	HbA1c (%): 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/m²): 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 ^{9;10}	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	HbA1c (%): 7.2 SD0.4 to 0.5	Comparator: placebo	FPG (mmol/L): -0.95 (-1.33, -0.57)
Duration: 24 weeks	BMI (kg/m ²): 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 ¹¹	N: 801	Intervention: dapagliflozin once daily	HbA1c (%): 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	HbA1c (%): 7.7 SD0.9	Comparator: glipizide (mean dose	FPG (mmol/L): -0.20 (95% CI NR)
Duration: 52 weeks	BMI (kg/m²): 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 ¹²	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	HbA1c (%): 8.3 to 8.4 SD1.0	Comparator: placebo	FPG (mmol/L): -1.33 (95% CI NR)
Duration: 24 weeks	BMI (kg/m²): 51 to 62% \geq 30; 87 to 93%	Background antidiabetic therapy:	SBP (mmHg): -4.7 (95% CI NR)
Follow-up: 24 week extension	≥ <mark>25</mark>	pioglitazone (30 or 45 mg/day)	
<mark>Quality:</mark> low			
Strojek 2011 ¹³	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	HbA1c (%): 8.1 SD0.7 to 0.8	Comparator: placebo	FPG (mmol/L): -1.47 (-1.86, -1.08)
Duration: 24 weeks	BMI (kg/m ²): 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			

udy design	Participants	Interventions	Outcomes
/ilding 2009 ¹⁴	N : 71	Intervention: 10 or 20 mg dapagliflozin	HbA1c (%): -0.70 (-1.07, -0.33)
esign: multi-centre (n=26), 3-arm,	Age (years): 56 to 58 SD7 to 11	once daily	Weight (kg): -2.60 (-3.94, -1.26)
ouble blind, placebo controlled RCT	HbA1c (%): 8.4 to 8.5 SD0.7 to 0.9	Comparator: placebo	FPG (mmol/L): -0.86 (-2.13, +0.42)
uration: 12 weeks	BMI (kg/m²): 34.8 to 36.2 SD3.6 to 4.6	Background antidiabetic therapy:	SBP (mmHg): NR
ollow-up: 4 weeks		insulin (51 to 56 U) + OAD (≤79%	
uality: medium		metformin only, ≤25% metformin plus	
		TZD, ≤12.5% TZD only)	
/ilding 2012 ¹⁵	N: 800	Intervention: 2.5, 5 or 10 mg	HbA1c (%): -0.57 (-0.67, -0.40)
esign: 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)
puble blind, placebo controlled RCT	HbA1c (%): 8.5 to 8.6 SD0.8 to 0.9	Comparator: placebo	FPG (mmol/L): NR
uration: 24 weeks	BMI (kg/m ²): 33.0 to 33.4 SD5.0 to 5.9	Background antidiabetic therapy:	SBP (mmHg): -3.11 (-5.79, -0.43)
ollow-up: 24 + 56 week extension		insulin (77.1 U) ± OAD (~50% none,	
uality: high		~40% metformin only, rest combination)	
anagliflozin			Difference versus active / placebo (959
			CI)
osenstock 2012 ¹⁶	N: 451	Intervention: 50, 100, 200 or 300 mg OD	HbA1c (%): -0.48 to -0.73 vs placebo;
esign: 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)
ouble blind, placebo and active	HbA1c (%): 7.75 SD0.93	Comparator 1: placebo	Weight (kg): -1.2 to -2.3 vs placebo;
ontrolled RCT	BMI (kg/m²): 31.5 SD4.9	Comparator 2: 100 mg OD sitagliptin	-1.7 to -2.8 vs sitagliptin (95% CI NR)
uration: 12 weeks		Background antidiabetic therapy:	FPG (mmol/L): -1.1 to -1.7 vs placebo;
ollow-up: 2 weeks		metformin (≥1500 mg)	-0.2 to -0.8 vs sitagliptin (95% CI NR)
uality: medium			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]
		0/1/	

Table 2. Study quality – risk of bias assessment

Study	Sequence generation	Allocation concealment	Blinding	Adequate handling of incomplete outcome data	Total drop out from drug assignment	No selective reporting	Groups comparable at baseline	Adequate power	Funder
Dapagliflozin									
Bailey 2010 ⁸	Yes	Yes	Yes (double blind)	Yes – last observation carried forward	12%	Yes	Yes	Yes – 0.5% HbA1c difference detectable	Astra-Zeneca and Bristol- Myers-Squibb
Bolinder 2012 / Ljunggren 2012 ^{9;10}	Yes	Yes	Yes (double blind)	Yes – last observation carried forward	7.1%	Yes	Yes	Unclear for primary endpoint, 2% BMD difference detectable	Astra-Zeneca and Bristol- Myers-Squibb
Nauck 2011 ¹¹	Yes	Yes	Yes (double blind and double dummy)	Yes – last observation carried forward	22.1%	Yes	Yes	Yes - 0.35% HbA1c difference detectable	Astra-Zeneca and Bristol- Myers-Squibb
Rosenstock 2012 ¹²	Not reported	Not reported	Yes (double blind)	Not reported	8% at 24 weeks, 19% at 48 weeks	Yes	Unclear	Not reported	Astra-Zeneca and Bristol- Myers-Squibb
Strojek 2011 ¹³	Yes	Yes	Yes (double blind and double dummy)	Yes – last observation carried forward	8.5%	Yes	Yes	Yes – 0.5% HbA1c difference detectable	Astra-Zeneca and Bristol- Myers-Squibb
Wilding 2009 ¹⁴	Not reported	Not reported	Yes (single blind during lead in, double blind during study)	Yes – last observation carried forward	7.0%	Yes	Partially; matched for patient demographics, not for prior medications	Yes – 0.5% HbA1c difference detectable	Astra-Zeneca and Bristol- Myers-Squibb
Wilding 2012 ¹⁵	Yes	Yes	Yes (double blind and double dummy)	Yes – last observation carried forward	11% at 24 weeks, 15.5% at 48 weeks	Yes	Yes	Yes – 0.5% HbA1c difference detectable	Astra-Zeneca and Bristol- Myers-Squibb
Canagliflozin									
Rosenstock 2012 ¹⁶	Not reported	Not reported	Yes (double blind)	Yes – last observation carried forward	10.9%	Yes	Yes	Yes – 0.55% HbA1c difference detectable	Janssen Global Services

Clinical effectiveness

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

HbA1c levels

Figure 2 shows the results of the meta-analysis of 10 mg/day of dapagliflozin versus placebo for HbA1c for study durations up to 26 weeks and for 48 to 52 weeks. Figure 3 shows the reductions in HbA1c in the seven study groups of the canagliflozin study (Rosenstock 2012)¹⁶ after 12 weeks of treatment.

Dapagliflozin at a dose of 10 mg/day significantly reduced HbA1c by (WMD) -0.54% (95% CI: -0.67, -0.40, p<0.00001) after 12 to 26 weeks of treatment compared to placebo. There was significant heterogeneity, which was eliminated when excluding the only study with a baseline HbA1c <7.5% (Bolinder 2012)⁹. The WMD in HbA1c for studies with a baseline HbA1c value of >7.5% was -0.59% (95% CI: -0.67, -0.51). Change from baseline in the 10 mg dapagliflozin groups ranged between -0.39 and -0.96% (main study end), and differences to placebo between -0.29 and -0.69%. HbA1c reductions at 48 to 52 weeks were similar to those at up to 26 weeks (three studies, WMD -0.54, 95% CI: -0.69, -0.38, p<0.00001).

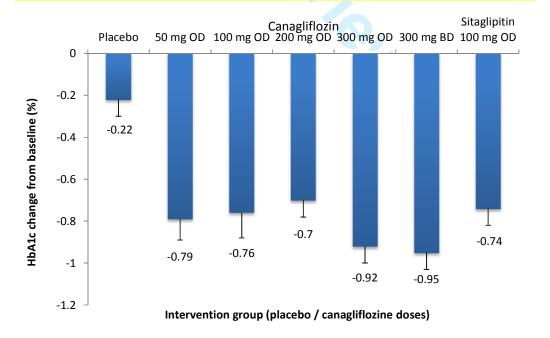
In the study by Nauck 2011,¹¹ there was no difference in HbA1c reduction between dapagliflozin and glipizide, both reducing HbA1c by -0.52% (95% CI: -0.60, -0.44).

Canagliflozin reduced HbA1c in a dose-related manner up to 300 mg once daily (HbA1c reductions from baseline ranging from -0.70 to 0.95%) after 12 weeks of treatment, with only a small difference between the once daily and twice daily doses at 300 mg (-0.92% SE0.08 and -0.95% SE0.08 from baseline, Figure 3). The HbA1c reduction from baseline with sitagliptin was -0.74% SE0.08.

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

	Dapaglif	lozin (10 r	ng)	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]	-
Wilding 2012 Subtotal (95% CI)	-0.96	0.67	173 701	-0.39	0.72	166 687	12.5% 63.9%	-0.57 [-0.72, -0.42] -0.54 [-0.67, -0.40]	-
Heterogeneity: Tau ² = Test for overall effect:	,	,	5 (P = 0).006); l² = 7	0%				
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]	•
Heterogeneity: Tau ² = Test for overall effect:	,	,	2 (P = 0.0	05); I ² = 66%	6				
Total (95% CI)			1084			1060	100.0%	-0.54 [-0.63, -0.44]	•
Heterogeneity: Tau ² =	0.01; Chi ² = 2	22.81, df =	8 (P = 0).004); I ² = 6	5%			-	-1 -0.5 0 0.5
Test for overall effect:	Z = 10.99 (P	< 0.00001)					Fa	vours dapagliflozin Favours placel
rest for overall chest.				0.55), $I^2 = 0$	0/			I a	vouis uapagiilloziii T avouis piacei

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

Dapaglif	lozin (10	mg)	PI	acebo			Mean Difference	Mean Difference
Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
-2.9	2.62	133	-0.9	2.95	136	10.5%	-2.00 [-2.67, -1.33]	
-2.96	2.61	89	-0.88	2.62	91	8.3%	-2.08 [-2.84, -1.32]	
-0.14	2.3	140	1.64	2.3	139	14.8%	-1.78 [-2.32, -1.24]	
-2.26	1.5	151	-0.72	1.47	145	27.8%	-1.54 [-1.88, -1.20]	
-4.5	2.31	23	-1.9	2.26	22	3.0%	-2.60 [-3.94, -1.26]	
-1.61	2.51	177 713	0.43	2.51	168 701	15.2% 79.5 %	-2.04 [-2.57, -1.51] -1.81 [-2.04, -1.57]	•
ore								
-4.39	4.14	81	-2.03	4.03	84	3.4%	-2.36 [-3.61, -1.11]	
0.69	3	140	2.99	3.4	139	8.5%	-2.30 [-3.05, -1.55]	
-1.61	3.48	166	0.82	3.39	157	8.6%	-2.43 [-3.18, -1.68]	_
		387			380	20.5%	-2.36 [-2.85, -1.88]	•
0.00; Chi ² =	: 0.06, df =	= 2 (P =	0.97); I	$^{2} = 0\%$				
Z = 9.49 (P	< 0.00001	1)						
		1100			1081	100.0%	-1.95 [-2.18, -1.71]	♦
0.02; Chi ² =	9.69, df =	= 8 (P =	0.29); 1	² = 17 ⁹	%			4 -2 0 2
,		,					F	avours experimental Favours control
rences: Chi	$^{2} = 4.33$ c	f = 1/P	= 0.04	\ I ² = 7	76 0%		•	
	-2.9 -2.96 -0.14 -2.26 -4.5 -1.61 -0.01; Chi² = 7 -4.39 -0.69 -1.61 -0.00; Chi² = 7 -2.96 -1.61 -2.26 -4.50 -1.61 -4.39 -1.61 -4.39 -1.61 -4.39 -1.61 -4.39 -1.61	-2.9 2.62 -2.96 2.61 -0.14 2.3 -2.26 1.5 -4.5 2.31 -1.61 2.51 0.01; Chi² = 5.30, df = 2 = 15.17 (P < 0.0000) ore -4.39 4.14 0.69 3 -1.61 3.48 0.00; Chi² = 0.06, df = 2 = 9.49 (P < 0.0000) 0.02; Chi² = 9.69, df = 2 = 16.17 (P < 0.0000)	-2.9 2.62 133 -2.96 2.61 89 -0.14 2.3 140 -2.26 1.5 151 -4.5 2.31 23 -1.61 2.51 177 713 0.01; Chi² = 5.30, df = 5 (P = 2 = 15.17 (P < 0.00001) ore -4.39 4.14 81 0.69 3 140 -1.61 3.48 166 387 0.00; Chi² = 0.06, df = 2 (P = 2 = 9.49 (P < 0.00001) 1100 0.02; Chi² = 9.69, df = 8 (P = 2 = 16.17 (P < 0.00001)	Mean SD Total Mean -2.9 2.62 133 -0.9 -2.96 2.61 89 -0.88 -0.14 2.3 140 1.64 -2.26 1.5 151 -0.72 -4.5 2.31 23 -1.9 -1.61 2.51 177 0.43 713 0.01; Chi² = 5.30, df = 5 (P = 0.38); F 2 = 15.17 (P < 0.00001)	Mean SD Total Mean SD -2.9 2.62 133 -0.9 2.95 -2.96 2.61 89 -0.88 2.62 -0.14 2.3 140 1.64 2.3 -2.26 1.5 151 -0.72 1.47 -4.5 2.31 23 -1.9 2.26 -1.61 2.51 177 0.43 2.51 713 713 713 713 713 713 713 714 715 715 716 717 717 718	Mean SD Total Mean SD Total -2.9 2.62 133 -0.9 2.95 136 -2.96 2.61 89 -0.88 2.62 91 -0.14 2.3 140 1.64 2.3 139 -2.26 1.5 151 -0.72 1.47 145 -4.5 2.31 23 -1.9 2.26 22 -1.61 2.51 177 0.43 2.51 168 713 701 0.01; Chi² = 5.30, df = 5 (P = 0.38); I² = 6% Z = 15.17 (P < 0.00001)	Mean SD Total Mean SD Total Weight -2.9 2.62 133 -0.9 2.95 136 10.5% -2.96 2.61 89 -0.88 2.62 91 8.3% -0.14 2.3 140 1.64 2.3 139 14.8% -2.26 1.5 151 -0.72 1.47 145 27.8% -4.5 2.31 23 -1.9 2.26 22 3.0% -1.61 2.51 177 0.43 2.51 168 15.2% 713 701 79.5% 0.01; Chi² = 5.30, df = 5 (P = 0.38); l² = 6% 2 2 3.39 157 8.6% 2 = 15.17 (P < 0.00001)	Nean SD Total Nean SD Total Weight IV, Random, 95% CI -2.9 2.62 133 -0.9 2.95 136 10.5% -2.00 [-2.67, -1.33] -2.96 2.61 89 -0.88 2.62 91 8.3% -2.08 [-2.84, -1.32] -0.14 2.3 140 1.64 2.3 139 14.8% -1.78 [-2.32, -1.24] -2.26 1.5 151 -0.72 1.47 145 27.8% -1.54 [-1.88, -1.20] -4.5 2.31 23 -1.9 2.26 22 3.0% -2.60 [-3.94, -1.26] -1.61 2.51 177 0.43 2.51 168 15.2% -2.04 [-2.57, -1.51] -7.01 79.5% -1.81 [-2.04, -1.57] -0.01; Chi² = 5.30, df = 5 (P = 0.38); I² = 6% -2.15.17 (P < 0.00001)

Systolic blood pressure

Dapagliflozin produced a reduction in systolic blood pressure at all doses (p-values generally not reported) ranging from -1.3 to -7.2 mmHg in the 10 mg dapagliflozin groups compared to changes of +2.0 to -0.11 mmHg in the control groups. Rosenstock (2012) reported a systolic blood pressure reduction in response to canagliflozin ranging from -0.9 SE1.7 mmHg with 50 mg OD to -4.9 SE1.5 mmHg with 300 mg OD (-1.3 SE1.5 mmHg with placebo, -0.8 SE1.4 mmHg with sitagliptin).¹⁶

Fasting plasma glucose (FPG)

A significant reduction in FPG was seen in all dapagliflozin groups compared to placebo, with 10 mg dapagliflozin reducing FPG between -0.86 and -1.47 mmol/L more than control. There was no significant difference between FPG reductions with dapagliflozin versus glipizide in the study by Nauck 2011.¹¹

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

Adverse events

Urinary and genital tract infection

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

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

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

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

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

Hypoglycaemia

Overall, there was no significant difference in all types of hypoglycaemia between dapagliflozin and placebo groups. Hypoglycaemia, where data permitted, was divided into three categories: severe, moderate and other, corresponding respectively to capillary

glucose readings of; <3.0 mmol/L (with external assistance required), <3.5 mmol/L, and symptoms suggestive of hypoglycaemia, but without confirming capillary glucose measurement. The incidence of all forms hypoglycaemia in the dapagliflozin groups ranged from 1.1% (Rosenstock 2012) to 56.6%. (Wilding 2012, any dose of dapagliflozin + insulin ± OAD).

Wilding 2009, reported more than a doubling of all hypoglycaemic events when dapagliflozin and insulin were compared to placebo and insulin (27% compared to 13%), but with only 16 hypoglycaemic episodes in a total of 71 participants. ¹⁴ Strojek 2011 reported a small, dose independent, increase in hypoglycaemia from dapagliflozin 2.5 mg, 5 mg and 10 mg, producing hypoglycaemia rates of 7.1%, 7.5% and 7.9% respectively, compared to 4.7% for placebo and glimepiride, however again with only a small number hypoglycaemic events, 29 amongst 592 participants. ¹³ Nauck 2011 reported that compared to glipizide, dapagliflozin produced a significant reduction in all types of hypoglycaemic events, with an incidence of 3.4% compared to 39.7% (14 versus 162 events). ¹¹

Rosenstock 2012, comparing placebo to canagliflozin, found a hypoglycaemic event rate of 2% in the placebo group, of 0 to 6% in the canagliflozin groups (highest rate in the 200 mg once daily group, no dose dependence), and 5% in the sitagliptin group. The severity was not commented on.¹⁶

Other adverse events

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

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. ¹⁷ Nauck (2011) in one of the largest studies (801 participants), found a significantly higher incidence of hypoglycaemia in the sulphonylurea group, than with dapagliflozin. Hypoglycaemia in patients treated with SGLT2 receptor inhibitors was seen to be greatest when used in combination with insulin.

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

Implications for future practice

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

Metformin

- The sulphonylureas
- Pioglitazone
- Acarbose
- The meglitinide analogues, nateglinide and repaglinide
- The GLP-1 analogues
- The DPP-4 inhibitors
- The SGLT inhibitors
- Insulins

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

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

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

Limitations of studies reviewed

There are no long term data on SGLT2 side effects, both in terms of rare complications yet to be identified, but also on the long term effects of significant glycosuria on the urinary tract. Two extension studies, published at present only as conference abstracts, reported that weight loss was maintained to two years. Del Prato and colleagues¹⁸), 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 colleagues¹⁹) in a follow-up of 64% of original participants, reported that by two years, weight had increased by 1.8kg in the placebo group but had decreased by 1.4kg in the 10mg dapagliflozin group.

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

Data of canagliflozin come from only one paper. Only two studies (Wilding 2009 and 2012) examined use of dapagliflozin in triple therapy, with insulin, and no trials examined the role of the SGLT2 receptor inhibitors in triple oral therapy.

The costs of the drugs are not yet known so cost-effectiveness cannot be assessed. The sulphonylureas are now very low cost, so the SGLT2 receptor inhibitors are very unlikely to be cost-effective compared to them. They are likely to be used in patients in whom metformin and sulphonylureas are insufficient or not tolerated, so the main comparators may be the gliptins, which have similar effects on HbA1c, are weight-neutral and which also increase the risk of UTIs, by about 40%. ²¹

Musso et al. (2012)²¹ produced a systematic review of SGLT2 inhibitors that included 13 articles. The main reasons for the difference between our own review and that of Musso et al. is our focus on a real world use of SLGT2 inhibitors, and inclusion of recent trials. We excluded studies of less than eight weeks in duration, whilst Musso et al. analysed studies as short as two weeks. In addition, Musso et al. included studies with SGLT2 inhibitors are primary intervention, whilst the present study has only looked at SGLT2 inhibitors as in combination therapy.

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

The US Food and Drug Administration (FDA) reviewed dapagliflozin in July 2011.22 They felt unable to approve it without additional safety data, mainly because of concerns about bladder and breast cancer. In the study data, there were nine cases of breast cancer in the dapagliflozin groups and none in the control groups. Some of these cancers occurred not long after dapagliflozin had been started. The absence of breast cancers amongst the controls was considered unexpected. An analysis by the manufacturers gave a standardised incidence ratio of 1.27 (95% CI: 0.58, 2.41) but this was not sufficient to reassure the FDA

committee. There were nine cases of bladder cancer in those taking dapagliflozin and only one in the control groups, though it was noted that in five cases, haematuria had been recorded before dapagliflozin was started. The FDA committee noted that the imbalance might possibly be due to detection bias. The committee voted 9 to 6 against approval.

CONCLUSIONS

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

Contributions

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

Competing interests

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

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REFERENCES

- (1) Diabetes UK. Diabetes in the UK: Key statistics on diabetes. http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf . 2010. Accessed: 2-8-2012.
- (2) Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003; 289(1):76-79.
- (3) Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB et al. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. The MILIS Study Group. J Am Coll Cardiol 1989; 14(1):49-57.
- (4) Santer R, Kinner M, Lassen CL, Schneppenheim R, Eggert P, Bald M et al. Molecular analysis of the SGLT2 gene in patients with renal glucosuria. *J Am Soc Nephrol* 2003; 14(11):2873-2882.
- (5) Hanefeld M, Forst T. Dapagliflozin, an SGLT2 inhibitor, for diabetes. *Lancet* 2010; 375(9733):2196-2198.

- (6) Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. http://www.cochrane-handbook.org/. 2011. The Cochrane Collaboration. Accessed: 9-8-2012.
- (7) WHO. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. WHO/NCD/NCS/99.2. 1999. http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf. Accessed: 9-8-2012.
- (8) Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010; 375(9733):2223-2233.
- (9) Bolinder J, Ljunggren O, Kullberg J, Johansson L, Wilding J, Langkilde AM et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *J Clin Endocrinol Metab* 2012; 97(3):1020-1031.
- (10) Ljunggren O, Bolinder J, Johansson L, Wilding J, Langkilde AM, Sjostrom CD et al.

 Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin.

 Diabetes Obes Metab 2012; 9999(9999).
- (11) Nauck MA, Del PS, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care* 2011; 34(9):2015-2022.
- (12) Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of Dapagliflozin, an SGLT2 Inhibitor, on HbA1c, Body Weight, and Hypoglycemia Risk in Patients With Type 2 Diabetes Inadequately Controlled on Pioglitazone Monotherapy. *Diabetes Care* 2012; 35(7):1473-1478.
- (13) Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab* 2011; 13(10):928-938.
- (14) Wilding JP, Norwood P, T'joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. *Diabetes Care* 2009; 32(9):1656-1662.
- (15) Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med* 2012; 156(6):405-415.
- (16) Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care* 2012; 35(6):1232-1238.
- (17) Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L et al. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. *Clin Pharmacol Ther* 2009; 85(5):520-526.

- (18) Del Prato S, Nauck MA, Rohwedder K, Theuerkauf A, Langkilde AM, Parikh S. Long-term efficacy and safety of dapagliflozin vs add-on glipizide in patients with type 2 diabetes inadequately controlled with metformon: 2 year results. 47th Annual Meeting of Eureopan Association for the Study of Diabetes, Lisbon September 2011; S348
- (19) Wilding JP, Woo VC, Rohwedder K, Sugg JE, Parikh SJ. Long-term effectiveness of dapagliflozin over 104 weeks in patients with type 2 diabetes poorly controlled with insulin. 72nd Scientific Session of the American Diabetes Association June 2012: A267-268
- (20) Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, Philip S. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. *Health Tech Assessment 2010;14: no 36*
 - (21) Musso G, Gambino R, Cassader M, Pagano G. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. *Ann Med* 2012; 44(4):375-393.
 - (22) Food and Drug Administration. Summary minutes of the endocronologic and metabolic drugs advisory committee. 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM262990.pdf. Accessed: 9-8-2012.

Appendix - Detailed study data

Dapagliflozin

	JL, Pieters A, Bastien A, List JF. Effect of dapagli andomised, double-blind, placebo-controlled tr		vho 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 typ	oe 2 diabetes in patients with inadequate	HbA1c control with metformin alone						
Study quality	High – see quality table for further informatio	n							
Study	Multi-centre: 80 (USA, Canada, Argentina, Me	exico, Brazil)							
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							
	Design: 4-arm parallel-group RCT, double blin	d, placebo controlled							
	Primary outcome: change from baseline in Hk	oA1c at week 24							
	Secondary outcomes:								
	At 24 weeks changes in:								
	- Fasting plasma glucose								
	- Proportion of patients achieving HbA1c <7%, number with HbA1c of 9% or more								
	- Total bodyweight, change from baseline	in bodyweight, and decreases in bodywe	eight of 5% or more						
	- Laboratory tests, adverse events								
Participant	N: 534 analysed								
criteria	Inclusion criteria: participants aged between	18 and 77 years; type 2 diabetes; BMI ≤4	I5 kg/m²; HbA1c 7 to 10.0%; fasting C-peptide	e ≥0.34 ng/ml; taking stable dose					
	metformin ≥1500 mg per day								
	Exclusion criteria: serum creatinine ≥133 μmo								
	AST or ALT >three times the upper limit of normal; creatine kinase >three times the upper limit of normal, symptoms of poorly controlled diabetes (including marked								
	polyuria and polydipsia with >10% weight loss during the 3 months before enrolment); systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg; any								
	significant other systemic disease								
Interventions	Intervention 1: 2.5 mg dapagliflozin + metfori								
	Intervention 2: 5 mg dapagliflozin + metformin								
	Intervention 3: 10 mg dapagliflozin + metformin								
	Intervention 4: matching placebo + metformin								
	OAD schedule: metformin at pre-study dose (≥1500 mg/day; mean dose 1792 to 1861 mg/day); dapagliflozin once daily before morning meal								
	All groups: diet and exercise counselling Lead in period: 2 weeks, single blind, to assess compliance with placebo, patients randomised after successful completion; metformin dose (open label 500 mg tablets)								
		ss 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	Age: 55.0 SD9.3 years	Age: 54.3 SD9.4 years	Age: 52.7 SD9.9 years					
	Sex: 55% male	Sex: 51% male	Sex: 50% male	Sex: 57% male					

Headache n=6

	BMI (kg/m²): 31.	8 SD5.3	BMI (kg/m	BMI (kg/m ²): 31.6 SD4.8		BMI (kg/m ²): 31.4 SD5.0		BMI (kg/m²): 31.2 SD5.1 HbA1c (%): 7.92% SD0.82	
				7.99% SD0.90	HbA1c (%): 8.17% SD0.96		HbA1c (%): 7		
	Duration of diabetes: 5.8 SD5.1 years			Duration of diabetes: 6.0 SD6.2 years		Duration of diabetes: 6.4 SD5.8 years		Duration of diabetes: 6.1 SD5.4 years	
	FPG (mmol/L): 9	.19 SD2.57	FPG (mmo	I/L): 8.96 SD2.39	FPG (mmd	ol/L): 9.39 SD2.72	FPG (mmol/L	.): 8.66 SD2.15	
	Systolic BP (mml	Hg): 127.7 SD14.6	Systolic BP	(mmHg): 126.6 SD14.5	Systolic B	P (mmHg): 126.9 SD14.3	Systolic BP (r	nmHg): 126.0 SD15.9	
Outcome (chan	ge from baseline to	o study end (week 24))							
	Group 1 (n=134):	1	Group 2 (n	=135):	Group 3 (ı	n=133):	Group 4 (n=1	32):	
	Placebo OD + me	etformin	2.5 mg dap	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	-0.70	-0.85 to -0.56	-0.84	-0.98 to -0.70	
				p=0.0002 vs placebo		p<0.0001 vs placebo		p<0.0001 vs placebo	
ΔWeight (kg)	-0.9	-1.4 to -0.4	-2.2	-2.7 to -1.8	-3.0	-3.5 to -2.6	-2.90	-3.3 to -2.4	
				p<0.0001 vs placebo		p<0.0001 vs placebo		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	
Salety assessing		aemia = symptomatic episc				 via patient questionnaire and vents – where frequency is 		or more adverse event	
		aemia = symptomatic episc aemia = symptomatic episc			Seneral e	vents – where frequency is			
		ery, capillary glucose <3.0m		xterrial assistance with		ary Tract Infection	Group 1 = n=88 Group 2 = n=89		
	Tollowing recove	ery, capillary glucose <5.0111	IIIOI/L			ital Tract Infection	Group 3 = n=		
					HypoT = Hypotension HypoG = Hypoglycaemia		Group 4 = n=98		
	Group 1 (n anal	vsod=134)·	Group 2 (n	= 135).	Group 3 (ı		Group 4 (n= 132):		
	Placebo OD + m			agliflozin OD + metformin		ngliflozin OD + metformin		liflozin OD + metformin	
Specific events			UTI n= 6, G				UTI n=16, GT		
opeome events	HypoT n=1, Hyp			, HypoG n=3	UTI n=10, GTI n=18 HypoT n=2, HypoG n=5		HypoT n=0, HypoG n=5		
	,, ,,	o discontinuation n=5	/ / /	ding to discontinuation n=3	/ .	ding to discontinuation n=3	Events leading to discontinuation n=4		
	Diarrhoea n=7		Diarrhoea		Diarrhoea		Diarrhoea n=	<u> </u>	
	Back pain n=7		Back pain r	-	Back pain		Back pain n=1		
	Nasopharyngitis	n=11		ngitis n=12		yngitis n=4	Nasopharyng		
	Cough n=7		Cough n=4	•	Cough n=4	, •	Cough n=1	•	
	Influenza n=10		Influenza n		Influenza		Influenza n=8	}	
	Hypertension n=	=6	Hypertensi	-	Hypertens		Hypertension		
	Upper resp. trac		/ / /	o. tract Infection n=5	/ .	p. tract Infection n=4	, · ·	ract Infection n=3	
	Handalahan C		11		11	•	U a a da ala a		

Headache n=11

Headache n=1

Headache n=4

and regional adipo	en Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, Sugg J, Parikh S. Effects of dapagliflozin on body weight, total fat mass, se tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. Journal of orgy and Metabolism 2012; 97(3): 1020-1031 ⁹	Funding source: Astra-Zeneca and Bristol-Myers-Squibb SGLT2 inhibitor (10 mg dapagliflozin)
resorption or bone	der J, Johansson L, Langkilde AM, Sjöström CD, Sugg J, Parikh S. Dapagliflozin has no effect on markers of bone formation and mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes, Obesity and E-publication ahead of print] ¹⁰	+ metformin versus placebo + metformin
Aim: to confirm we metformin	ight loss with dapagliflozin, and establish effect on body composition and bone metabolism in patients with type 2 diabetes with	inadequate glucose control with
Study quality	High – see quality table for further information	
Study particulars	Multi-centre: 40 (Bulgaria, Czech Republic, Hungary, Poland, Sweden) Duration of intervention: 24 weeks Duration of run in: 2 weeks Follow-up: 78 week extension period	
	Design: 2-arm parallel group RCT, double blind, placebo controlled Primary outcome: change from baseline in total body weight at week 24 Secondary outcomes:	
	At week 24: Change in waist circumference and total fat mass Proportion achieving weight reduction of >5% HbA1c, fasting plasma glucose Markers of bone formation and resorption	
	 DXA assessment of bone mineral density and body composition Systolic and diastolic blood pressure Adverse events, laboratory values 	
Participant criteria	N: 180 analysed Inclusion criteria: participants with type 2 diabetes; postmenopausal women aged 55 to 75 years or men aged 30 to 75 years; BMI ≥25 kg/m²; weight ≤120 kg; treatment exclusively with a stable dose of metformin ≥1500 mg/day for at least 12 weeks bef Exclusion criteria: men <30 years, perimenopausal women, HbA1c >8.5%, use of insulin within 6 months (except temporary ≤7 months; calculated creatinine clearance <60 mL/min; urine albumin:creatinine ratio >1800 mg/g (>203.4 mg/mmol); ASP and/a 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 skeld similar within 6 months of enrolment; SBP ≥180 mmHg and/or DBP ≥110 mmHg; congenital renal glycosuria; significant cardiact haematological, oncological, endocrine, immunological (including hypersensitivity to study medications), and alcohol and/or su and/or lactation; a history of bariatric surgery; use of weight loss medication within 30 days of enrolment	fore enrolment days); body weight change >5% within 3 ALT and/or creatine kinase ≥3 times g/dL) for women; abnormal thyroid etal problems; metabolic bone disease or c, renal, hepatic, respiratory,
Interventions	Intervention 1: 10 mg dapagliflozin + metformin Intervention 2: placebo + metformin OAD schedule: metformin at pre-study dose (≥1500 mg/day, mean dose 1901 mg SD430 in Group 1, 1989 mg SD477 in Group 2 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	2); dapagliflozin once daily before or with

Participant	Group 1 (start n= 91, analysed n	=91): Placebo + metformin	Group 2 (start n= 91, analysed n= 89): 10 mg dapagliflozin + metformin					
baseline data	Age: 60.8 SD6.9 years		Age: 60.6 SD8.2 years					
	Sex: 56% male	ex: 55.1% male						
	BMI (kg/m ²): 31.7 SD3.9		BMI (kg/m ²): 32.1 SD3	<mark>3.9</mark>				
	HbA1c (%): 7.16% SD0.53			<mark>).44</mark>				
	Duration of diabetes: 5.5 SD5.3 y	<mark>years</mark>	Duration of diabetes:	6.0 SD4.5 year	r <mark>s</mark>			
	FPG (mmol/L): 8.3 SD1.4		FPG (mmol/L): 8.2 SD	1.4				
Outcome (change	from baseline to study end (24 wee	ks))						
	Group 1 (n=91): Placebo + metfo	<mark>rmin</mark>	Group 2 (n= 89): 10 m	Group 2 (n= 89): 10 mg dapagliflozin + metformin				
	Mean	95% CI	<mark>Mean</mark>	95% CI				
ΔHbA1c (%)	-0.10	-0.01 to -0.19 [from graph]	-0.39	-0.29 to -0.4	19 [from graph] , p<0.0001 vs placebo			
ΔWeight (kg)	-0.88	-1.43 to -0.34	<mark>-2.96</mark>	-3.51 to -2.4	1, p<0.0001 vs placebo			
ΔFPG (mmol/L)	+0.13	NR A	-0.82	NR, p<0.000	01 vs placebo			
	Mean	SD	Mean	SD				
ΔSBP (mmHg)	0.1	NR	<mark>-2.7</mark>	NR				
Adverse events	<u> </u>							
Safety assessment	t: assessed via adverse events from t	he Medical Dictionary or Regulatory Activities (N	MedDRA v12.1) via patier	nt questionnai	re and active questioning during visits, laborator			
tests and vital sign								
	Minor hypoglycaemia (HypoM) =	symptomatic episode, capillary glucose	General events – whe	re	At least one or more adverse event			
	<3.5mmol/L, asymptomatic episo		frequency is >2%		Group 1 = 42.9%			
		symptomatic episode needing external	UTI = Urinary Tract Infection GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe) 1 death in dapagliflozin group, no deaths in dapagliflozin group.					
	assistance with capillary glucose	<3.0mmol/L, recovery following glucose or						
	glucagon administration							
	Other hypoglycaemia (HypoO) =	symptoms, but without confirmative	HypoM = Hypoglycaemia (mild) HypoO = Hypoglycaemia other HypoT = Hypotension No significant effect on bone for		placebo group			
	measurement							
					No significant effect on bone formation and			
					resorption or bone mineral density			
	Group 1 (n=91): Placebo + metfo	<mark>rmin</mark>	Group 2 (n= 89): 10 m	g dapagliflozir				
Specific events	Group 1 (n=91): Placebo + metfo UTI n=2, GTI n=0	<mark>rmin</mark>	Group 2 (n= 89): 10 m UTI n=6, GTI n=3	g dapagliflozir				
Specific events			UTI n=6, GTI n=3					
Specific events	UTI n=2, GTI n=0							
Specific events	UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO r	n=1	UTI n=6, GTI n=3 HypoM n=2, HypoS n= HypoT n=1	0, HypoO n=0	+ metformin			
Specific events	UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO r HypoT n=0	n=1	UTI n=6, GTI n=3 HypoM n=2, HypoS n=	0, HypoO n=0	+ metformin			
Specific events	UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO r HypoT n=0 Events leading to discontinuation	n=1	UTI n=6, GTI n=3 HypoM n=2, HypoS n= HypoT n=1 Events leading to disco	0, HypoO n=0	+ metformin			
Specific events	UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO r HypoT n=0 Events leading to discontinuation Nasopharyngitis n=5	n=1	UTI n=6, GTI n=3 HypoM n=2, HypoS n= HypoT n=1 Events leading to disco	0, HypoO n=0	+ metformin			
Specific events	UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO r HypoT n=0 Events leading to discontinuation Nasopharyngitis n=5 Hypertension n=4	n=1	UTI n=6, GTI n=3 HypoM n=2, HypoS n= HypoT n=1 Events leading to disco Nasopharyngitis n=6 Hypertension n=4	0, HypoO n=0	+ metformin			
Specific events	UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO n HypoT n=0 Events leading to discontinuation Nasopharyngitis n=5 Hypertension n=4 Pneumonia n=0	n=1	UTI n=6, GTI n=3 HypoM n=2, HypoS n= HypoT n=1 Events leading to disco Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=3	0, HypoO n=0	+ metformin			
Specific events	UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO n HypoT n=0 Events leading to discontinuation Nasopharyngitis n=5 Hypertension n=4 Pneumonia n=0 Angina pectoris n=0	n=1	UTI n=6, GTI n=3 HypoM n=2, HypoS n= HypoT n=1 Events leading to disco Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=3 Angina pectoris n=2	0, HypoO n=0	+ metformin			
Specific events	UTI n=2, GTI n=0 HypoM n=2, HypoS n=0, HypoO n HypoT n=0 Events leading to discontinuation Nasopharyngitis n=5 Hypertension n=4 Pneumonia n=0 Angina pectoris n=0 Cystitis n=1	n=1	UTI n=6, GTI n=3 HypoM n=2, HypoS n= HypoT n=1 Events leading to disco Nasopharyngitis n=6 Hypertension n=4 Pneumonia n=3 Angina pectoris n=2 Cystitis n=2	0, HypoO n=0	+ metformin			

Study Quality High Study particulars Min Du Du Fo De Pri Se Participant N: criteria Increte In	ceiving stable dose metformin or metformin and one other OAD at up to half m	ype 2 diabetes (HbA1c >6.5 and ≤10%); BMI ≤45kg/m²; fasting C-peptide ≥0.33 nmol/l						
Study Quality High Study particulars Min Du Du Fo De Pri Se Participant N: criteria Increte In	gh — see quality table for further information ulti-centre: 95 sites across 10 countries world-wide uration of intervention: 52 weeks uration of run in: 2 weeks ulti-centre: 95 sites across 10 countries world-wide uration of run in: 2 weeks uration of 20 weeks, 156 week extension esign: 2-arm parallel group RCT, double-blind rimary outcome: absolute change from baseline in HbA1c at week 52 econdary outcomes: Change in total body weight Proportion with hypoglycaemic episode Proportion of ≥5% total weight loss 801 analysed clusion criteria: participants aged 18 years and older; inadequately controlled to the ceiving stable dose metformin or metformin and one other OAD at up to half metricipants.	ype 2 diabetes (HbA1c >6.5 and ≤10%); BMI ≤45kg/m²; fasting C-peptide ≥0.33 nmol/l						
Study particulars M Du Fo De Pr Se Participant Criteria Inc rei	ulti-centre: 95 sites across 10 countries world-wide uration of intervention: 52 weeks uration of run in: 2 weeks uration of run in: 2 weeks ulti-centre: on completion of 52 weeks, 156 week extension esign: 2-arm parallel group RCT, double-blind rimary outcome: absolute change from baseline in HbA1c at week 52 econdary outcomes: Change in total body weight Proportion with hypoglycaemic episode Proportion of ≥5% total weight loss 801 analysed clusion criteria: participants aged 18 years and older; inadequately controlled to ceiving stable dose metformin or metformin and one other OAD at up to half m							
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Participant N: criteria Inc	ollow-up: on completion of 52 weeks, 156 week extension esign: 2-arm parallel group RCT, double-blind imary outcome: absolute change from baseline in HbA1c at week 52 econdary outcomes: Change in total body weight Proportion with hypoglycaemic episode Proportion of ≥5% total weight loss 801 analysed clusion criteria: participants aged 18 years and older; inadequately controlled to ceiving stable dose metformin or metformin and one other OAD at up to half m							
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Participant N: criteria Inc	cimary outcome: absolute change from baseline in HbA1c at week 52 condary outcomes: Change in total body weight Proportion with hypoglycaemic episode Proportion of ≥5% total weight loss 801 analysed clusion criteria: participants aged 18 years and older; inadequately controlled to ceiving stable dose metformin or metformin and one other OAD at up to half m							
Se Participant N: criteria Inc	Change in total body weight Proportion with hypoglycaemic episode Proportion of ≥5% total weight loss 801 analysed clusion criteria: participants aged 18 years and older; inadequately controlled to ceiving stable dose metformin or metformin and one other OAD at up to half m							
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criteria Inc	clusion criteria: participants aged 18 years and older; inadequately controlled to ceiving stable dose metformin or metformin and one other OAD at up to half m							
re	ceiving stable dose metformin or metformin and one other OAD at up to half m							
		naximal dose for up to 8 weeks prior to enrolling; FPG ≤15 mmol/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							
	· · · · · · · · · · · · · · · · · · ·	or women; abnormal TSH; systolic blood pressure ≥180 mmHg and/or diastolic blood						
	essure ≥110 mmHg; significant other disease							
	tervention 1: dapagliflozin + metformin (dapagliflozin mean dose 9.2 mg/day)							
	Intervention 2: glipizide + metformin (glipizide mean dose 16.4 mg/day)							
	OAD schedule: metformin 1500 to 2000 mg/day (median dose at enrolment 2000 mg/day); dapagliflozin started at 2.5 mg, up-titrated to maximum tolerable dose (up to 10 mg); glipizide started at 5 mg, up titrated to maximum tolerable dose (up to 10 mg); glipizide started at 5 mg, up titrated to maximum tolerable dose (up to 10 mg); glipizide started at 5 mg, up titrated to maximum tolerable dose (up							
	to 10 mg); glipizide started at 5 mg, up-titrated to maximum tolerable dose (up to 20 mg) All groups: diet and lifestyle advice							
	0 , ,	1500 to 2000 mg/day; 2 weeks single blind placebo lead in prior to randomisation						
	roup 1 (start n= 406, analysed n=400):	Group 2 (start n= 408, analysed n= 401):						
-	2 mg dapagliflozin + metformin	16.4 mg glipizide + metformin						
	ge: 58 SD9 years	Age: 59 SD10 years						
	ex: 55.3% male	Sex: 54.9% male						
	MI (kg/m²): 31.7 SD5.1	BMI (kg/m ²): 31.2 SD5.1						
	25 kg/m ² : 95%	$\geq 25 \text{ kg/m}^2 : 90.8\%$						
	30 kg/m²: 57%	≥ 30 kg/m²: 55.4%						
	bA1c (%): 7.7% SD0.9	HbA1c (%): 7.7% SD0.9						
	uration of diabetes: 6 SD5 years	Duration of diabetes: 7 SD6 years						
	PG (mmol/L): 9.0 SD2.1	FPG (mmol/L): 9.1 SD2.3						

	Group 1 (n=400): 9.2 mg dapagliflozin + me	tformin	Group 2 (n= 401): 16.4 mg glipizide + metformin				
	Mean 9	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 assessmen	t: assessed via adverse events from the Medical	l Dictionary or Regulatory Activities	(MedDRA v12.1) via patient questionnaire ar	nd active questioning during visits			
	Severe hypoglycaemia (HypoS) = symptoma	atic episode, needing external	General events – where frequency is	At least one or more adverse event			
	assistance with following recovery, capillary		≥3%	Group 1 = n=318			
	Minor hypoglycaemia (HypoM) = symptom	atic episode, capillary glucose	UTI = Urinary Tract Infection	Group 2 = n=318			
	<3.5mmol/L		GTI = Genital Tract Infection				
	Other hypoglycaemia (HypoO) = symptoms	, but without measurement	HypoS = Hypoglycaemia (severe)	No deaths in dapagliflozin group			
	confirming		HypoM = Hypoglycaemia (mild)	3 deaths in glipizide group			
			HypoO = Hypoglycaemia other	.her			
			HypoT = Hypotension				
	Group 1 (n=406): 9.2 mg dapagliflozin + me	tformin	Group 2 (n= 408): 16.4 mg glipizide + me	Group 2 (n= 408): 16.4 mg glipizide + metformin			
Specific events	UTI n=44, GTI n=50		UTI n=26, GTI n=11				
	HypoS n=0, HypoM n=7, HypoO 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=37 (0 de	ue to hypoglycaemia)	Events leading to discontinuation n=24 (6 due to hypoglycaemia)				
	Diarrhoea n=19		Diarrhoea n=26				
	Nausea n=14		Nausea n=15				
	Vulvovaginal mycotic infection 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				
	Influenza n=30		Influenza n=30				
	Arthralgia n=11		Arthralgia n=21	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. Effects of dapagliflozin, an SG 2 diabetes inadequately controlled in pioglitazone mor	LT2 inhibitor, on HbA1c, body weight, and hypoglycaemia otherapy. Diabetes Care 2012; 35: 1473-1478 ¹²	risk in Funding source: Astra-Zeneca and Bristol-Myers-Squibb						
			SGLT2 inhibitor (5 or 10 mg dapagliflozin) + pioglitazone versus placebo + pioglitazone						
Aim: to examine th	e safety and efficacy of dapagliflozin added to pioglitazo	ne in type 2 diabetes patients inadequately controlled on p	<mark>ioglitazone</mark>						
Study quality	Low – see quality table for further information								
Study particulars	Multi-centre: 105 (Argentina, Canada, India, Mexico,	P <mark>eru, Philippines, Taiwan, USA)</mark>							
	Duration of intervention: 24 weeks								
	Duration of run in: 2 weeks								
	Follow-up: 24 week extension period								
	Design: 3-arm parallel group RCT, double blind, placebo controlled								
	Primary outcome: change from baseline in HbA1c at week 24								
	Secondary outcomes:								
	At week 24, change from baseline in:								
	- Fasting plasma glucose								
	- Postprandial glucose Total body weight								
	- Total body weight - Blood pressure								
	Blood pressureAdverse events, laboratory values, vital signs								
Participant									
criteria	N: 420 analysed Inclusion criteria: participants with type 2 diabetes; age ≥18 years; fasting C-peptide ≥1.0 ng/mL; BMI ≤45 kg/m²; Group A: ≥12 weeks of pioglitazone 30 or 45 mg/day								
Criteria	Inclusion criteria: participants with type 2 diabetes; age ≥18 years; fasting C-peptide ≥1.0 ng/mL; BMI ≤45 kg/m ⁻ ; 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 \geq 8.0 and \leq 11.0% or had received \geq 8 weeks of metformin \leq 1700 mg/day or sulphonylurea \leq half maximal dose with HbA1c \geq 7.0 to \leq 11.0%, not more than on								
	oral antidiabetic medication; Group B underwent 10 week dose optimisation in which initial therapy was discontinued and pioglitazone 30 mg/day was started and								
	increased to 45 mg/day if possible; pre-randomisation HbA1c had to be ≥7.0 and ≤10.5%								
	Exclusion criteria: AST or ALT >2.5 times upper limit of normal; total bilirubin >2.0 mg/dL, serum creatinine ≥2.0 mg/dL, urine albumin/creatinine ratio >1800 mg/g,								
	calculated creatinine clearance <50 mL/min, congestive heart failure class III and IV								
Interventions	Intervention 1: 5 mg dapagliflozin + pioglitazone								
	Intervention 2: 10 mg dapagliflozin + pioglitazone								
	Intervention 3: placebo + pioglitazone								
	OAD schedule: open-label pioglitazone 30 or 45 mg/day; dapagliflozin once daily; in case of inadequate glycaemic control (FPG >270 mg/dL (week 4 to 8) or >240 mg/dL								
		s were eligible for open label rescue medication (metformi							
	All groups: diet and exercise counselling								
	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	Age: 53.5 SD11.4 years	Age: 53.2 SD10.9 years	Age: 53.8 SD10.2 years						
	Sex: 51.1% male	Sex: 55.3% male	Sex: 42.1% male						
	BMI: 61.2% ≥30 kg/m ² ; 87.8% ≥25 kg/m ²	BMI: $61.7\% \ge 30 \text{ kg/m}^2$; $86.5\% \ge 25 \text{ kg/m}^2$	BMI: $51.4\% \ge 30 \text{ kg/m}^2$; $92.9\% \ge 25 \text{ kg/m}^2$						
	HbA1c: 8.34% SD1.00	HbA1c: 8.40% SD1.03	HbA1c: 8.37% SD0.96						
	Duration of diabetes: 5.07 SD5.05 years	Duration of diabetes: 5.64 SD5.36 years	Duration of diabetes: 5.75 SD6.44 years						

	FPG (mmol/L): 8.92 SD2.61		FPG (mmol/L): 9.36 SD	<mark>02.89</mark>	FPG (mmol/L): 9.15 SD2.57		
Outcome (change	from baseline to study en	d)					
	Group 1 (n=139): Placebo + pioglitazone		Group 2 (n=141): 5 mg	dapagliflozin + pioglitazone	Group 2 (n=140): 10 mg dapagliflozin + pioglitazone		
	<mark>Mean</mark>	SE	Mean		Mean	SE	
ΔHbA1c (%)	wk 24: -0.42	0.08	-0.82	0.08, p=0.0007 vs placebo	-0.97	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	
ΔWeight (kg)	wk 24: +1.64	0.28	+0.09	0.28, p<0.0001 vs placebo	-0.14	0.28, p<0.0001 vs placebo	
	wk 48: +2.99	<mark>0.41</mark>	<mark>+1.35</mark>	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	-0.8	1.2, p NS	-3.4	1.2, p NS	
	wk 48: +2.0	1.2	<mark>-1.0</mark>	1.1, p NR	<mark>-2.2</mark>	0.7, p NR	
Adverse events				·			
Safety assessment	t: assessed at every visit, q	uestioning, laboratory to	ests and vital signs				
	Minor hypoglycaemia	(HypoM) = symptomation	episode, capillary glucose	General events – where	At	least one or more adverse event	
	<3.5mmol/L, asymptor	natic episode with gluco	se <3.5 mmol/L	e needing external y following glucose or GTI = Genital Tract Infection HypoS = Hypoglycaemia (severe HypoM = Hypoglycaemia (mild)		roup 1 = 66.9%	
			episode needing external			roup 2 = 68.1%	
	assistance with capillar	ry glucose <3.0mmol/L, r	ecovery following glucose or			<mark>roup 3 = 70.7%</mark>	
	glucagon administration						
	Other hypoglycaemia	(HypoO) = symptoms, bu	ut without confirmative				
	<mark>measurement</mark>			HypoO = Hypoglycaemia othe			
	Group 1 (n=139): Place	<mark>ebo + pioglitazone</mark>	Group 2 (n=141): 5 mg	<mark>dapagliflozin + pioglitazone</mark>	Group 2	(n=140): 10 mg dapagliflozin + pioglitazone	
Specific events	UTI n=11, GTI n=4		UTI n=12, GTI n=13		UTI n=7	, GTI n=12	
	Any hypoglycaemia n=	<mark>1, HypoS n=0</mark>	Any hypoglycaemia n=	<mark>3, HypoS n=0</mark>	Any hyp	oglycaemia n=0, HypoS n=0	
	Decreased renal functi	<mark>on n=1</mark>	Decreased renal functi	<mark>on n=2</mark>	Decreased renal function n=2		
	Events leading to disco	ntinuation n=5	Events leading to disco	ntinuation n=5	Events leading to discontinuation n=3		
	Dyslipidaemia n=9		Dyslipidaemia n=11			aemia n=16	
	Nasopharyngitis n=7		Nasopharyngitis n=7		Nasoph	<mark>aryngitis n=11</mark>	
	Diarrhoea n=6		Diarrhoea n=5		Diarrho	To the state of th	
	Back pain n=4		Back pain n=5		Back pa		
	Upper resp. tract infec	tion n=10	Upper resp. tract infec	tion n=10		esp. tract infection n=7	
	Headache n=10		Headache n=3		Headacl		
	Pain in extremity n=1		Pain in extremity n=10			extremity n=4	
	Oedema peripheral n=	<mark>9</mark>	Oedema peripheral n=	<mark>6</mark>	<mark>Oede</mark> ma	<mark>a peripheral n=3</mark>	

			e 2 diabetes who have inadequate glycaemi esity and Metabolism 2011; 13(10): 928-938 ¹						
				SGLT2 Inhibitor (2.5, 5, or 10 mg dapagliflozin)plus glimepiride versus placebo plus glimepiride					
Aim: to determi	ine the efficacy, safety and tolerability of da	pagliflozin treatment, as an add-on therapy t	o glimepiride, in patients with inadequately o	controlled type 2 diabetes who had bee					
treated with sul	phonylurea monotherapy								
Study quality	High – see quality table for further inform	nation							
Study	Multi-centre: 84 sites across 7 countries	world-wide							
particulars	Duration of intervention : 24 weeks								
	Duration of run in : 1 week for patients sy								
	Follow-up: on completion of 24 weeks, 2	4 week extension							
	Design: 4-arm parallel group RCT, double								
	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%								
		aseline in patients with BMI ≥27kg/m²							
	- Change in FPG								
Participant	N: 592 analysed		2 11 1 (11) 44 27 1 440 00() 5241 4451	, 2					
criteria			2 diabetes (HbA1c ≥7 to ≤10.0%); BMI ≤45kg/	m; on stable sulphonylurea dose (at					
		at least 8 weeks prior to enrolment); fasting		mal, 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	egriancy of factation, use of weight loss med	ication within 30 days						
interventions		+ glimeniride							
	Intervention 2: 2.5 mg/day dapagliflozin + glimepiride Intervention 3: 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								
		lusion review for those switched to 4 mg/day	-	The meaner and more cashing private and account					
	Ferreal _ week for merasion, exc		Group 3 (n= 145)	Group 4 (n= 151)					
Participant	Group 1 (n= 146)	Group 2 (n= 154)							
•	Group 1 (n= 146) Placebo + glimepiride	Group 2 (n= 154) 2.5 mg dapagliflozin + glimepiride							
•	Placebo + glimepiride	2.5 mg dapagliflozin + glimepiride	5 mg dapagliflozin + glimepiride	10 mg dapagliflozin + glimepiride					
Participant baseline data		· · · · · · · · · · · · · · · · · ·							

	kg/m² H bA :		HbA1c: 8.11% SD0.75		HbA1c: 8.12% SD0.78		HbA1c: 8.07% SD0.79	
	HbA1c: 8.15%	HbA1c: 8.15% SD0.74 Duration of d		ion of diabetes: 7.7 SD6.0 years Duration of diabetes: 7.4 SD5.7 years		Duration of diabetes: 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 (change	ge from baseline	to study end (week 24))						
	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		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	-0).	-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	, 6r	General events – where frequency is ≥3% in any group UTI = Urinary Tract Infection GTI = Genital Tract Infection Hypo = Hypoglycaemia	At least one or more adverse event Group 1 = n=69; Group 2 = n=80 Group 3 = n=70; Group 4 = n=76 1 death in dapagliflozin 2.5 mg 1 death in dapagliflozin 10 mg
	Group 1 (n= 146)	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

	pod P, T'joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of sensitizers. Applicability of a novel insulin-independent treatment. Diabetes Care 2009; 32(9): 1656-1662 ¹⁴	Funding source: Astra-Zeneca and Bristol-Myers-Squibb
		SGLT2 Inhibitor (10 or 20 mg
		dapagliflozin) + insulin + OAD
		versus placebo + insulin + OAD
	if dapagliflozin lowers HbA1c in patients with type 2 diabetes poorly controlled with high insulin doses plus oral antidiabetic agent	TS .
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 stab	
	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, creatine kinase ≥3 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal, creatine kinase ≥3 times the upper limit of normal kinase the up	it 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); dapaglifloz	in 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 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 2 (n= 24): 10) mg dapagliflozin + OAD + insulin	Group 3 (n= 24): 2	20 mg dapagliflozin + OAD + insulin	
baseline data	Age: 58.4 SD6.5 years		Age: 55.7 SD9.2 yea	ars	Age: 56.1 SD10.6 years		
	Sex: 69.6% male		Sex: 54.2% male		Sex: 54.2% male		
	BMI (kg/m ²): 34.8 SD4.6	i	BMI (kg/m ²): 35.5 S	SD3.6	BMI (kg/m ²): 36.2	SD4.6	
	HbA1c: 8.40% SD0.9		HbA1c: 8.4% SD0.7		HbA1c: 8.5% SD0.	9	
	Duration of diabetes: 13	3.8 SD 7.3 years	Duration of diabete	es: 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	7 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	
	Minor hypoglycaemia =	, , , , ,		here frequency is >5%	At least one or more adverse event		
Adverse events		rse events, vital signs, laborato					
	capillary glucose <3.5mn	, , , , ,	UTI = Urinary Tract	• •	Group 2 = n=18		
	Major hypoglycaemia =		GTI = Genital Tract				
	, ,, ,,	nce with following recovery,	HypoT = Hypotension	on, HypoG = Hypoglycaemia	Group 3 = n=16		
	capillary glucose <3.0mn		HypoS = major hypo	11 41			
	Group 1 (n=23): Placebo) mg dapagliflozin + OAD + insulin	Group 3 (n= 24): 20 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	8, HypoS n=1	HypoT n=NR, Hypot	G n=7, HypoS n=0	HypoT n=NR, HypoG n=6, HypoS n=0		
	Events leading to discon	tinuation n=1	Events leading to d		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=	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 n		Dry Mouth n=2		
	Upper resp. tract Infection	on n=2	Upper resp. tract In	fection n=2	Nasopharyngitis n		
	Headache n= 2		Headache n=3		Peripheral oedem		
	Procedural pain n=2		Pharyngolaryngeal	pain n=2	Upper abdominal	pain n=1	
					Fatigue n=1		
					Influenza n=1		
				<u> </u>	Pain in extremity i	n=1	

			Upper resp.	tract Infection n=1
		r K, Parikh S. Long-term efficacy of dapaglifl s of Internal Medicine 2012; 156(6): 405-415	ozin in patients with type 2 diabetes mellitus	Funding source: Astra-Zeneca and Bristol-Myers-Squibb
				SGLT2 Inhibitor (2.5, 5 or 10 mg dapagliflozin) + insulin ± OAD versus placebo + insulin ± OAD
			adequately controlled with insulin with or wit	hout oral antidiabetic drugs
Study quality	High – see quality table for further inform	<mark>nation</mark>		
<mark>Study</mark>	Multi-centre: 126 worldwide			
<mark>particulars</mark>	Duration of intervention: 24 weeks			
	Duration of run in: 2 week enrolment			
		<mark>24 week extension plus further 56 week exte</mark>	nsion in progress	
	Design: 4-arm parallel group RCT, double			
	Primary outcome: change from baseline	in HbA1c to week 24		
	Secondary outcomes:			
	- Change in total body weight			
	- Change in calculated mean daily ins			
	 Proportion with mean daily insulin r Change in FPG 	reductions of \$10% from baseline		
	 Change in FPG Laboratory tests, adverse events, vi 	tal signs		
Participant	N: 800 analysed	tal signs		
criteria		ween 18 and 80 years; type 2 diabetes; RMI	45 kg/m²; inadequate glycaemic control (HbA	1c >7.5 to <10.5%); stable insulin regin
Citteria			Ds allowed (≥1500 mg metformin or maximur	
	dose of other OADS for ≥8 weeks)	eks, additional treatment with up to two OA	Ds allowed (21300 mg metrormin or maximur	in tolerated dose of at least flair maxim
	•	of poorly controlled diabetes: calculated cre	atinine clearance <50 ml/min per 1.73 m ² or s	serum creatinine >177 umol/L or if
	receiving metformin >133 µmol/L for me		definite cicarance 350 my min per 1:75 m or s	cram creatinine 2177 pmoly 2, or m
Interventions	Intervention 1: placebo + insulin ± OAD	2. 2. 2. 2. 2. p		
c. venerons	Intervention 2: 2.5 mg dapagliflozin + ins	sulin ± OAD		
	Intervention 3: 5 mg dapagliflozin + insu			
	Intervention 4: 10 mg dapagliflozin + ins			
			dose of insulin (mean daily dose 77.1 U) and	existing OADs (none in ~50%, metform
			5 to 6%); OAD doses could be decreased when	
	could be up-or down-titrated if needed			*
		et and exercise regimen; Lead in period: unc		
<mark>Participant</mark>	Group 1 (n analysed=193):	Group 2 (n=202):	Group 3 (n=211):	Group 4 (n=194):
<mark>baseline data</mark>	Placebo + insulin ± OAD	2.5 mg dapagliflozin + insulin ± OAD	5 mg dapagliflozin + insulin ± OAD	10 mg dapagliflozin + insulin ± OAD
	Age: 58.8 SD8.6 years	Age: 59.8 SD7.6 years	Age: 59.3 SD7.9 years	Age: 59.3 SD8.8 years
	Sex: 49.2% male	Sex: 49.5% male	Sex: 47.4% male	Sex: 44.8% male
			BMI (kg/m ²): 33.0 SD5.3	BMI (kg/m ²): 33.4 SD5.1
	BMI (kg/m ²): 33.1 SD5.9	BMI (kg/m²): 33.0 SD5.0		
	BMI (kg/m²): 33.1 SD5.9 HbA1c (%): 8.47% SD0.77	HbA1c (%): 8.46% SD0.78	HbA1c (%): 8.62% SD0.89	HbA1c (%): 8.57% SD0.82
	BMI (kg/m ²): 33.1 SD5.9			

	Systolic BP (mn	nHg): 136.1 SD17.2	Systolic BP (r	nmHg): 139.6 SD17.7	Systolic B	P (mmHg): 137.8 SD16.2	Systolic BP (I	Systolic BP (mmHg): 140.6 SD16.7		
Outcome (chan	ge from baseline	to study end)								
	Group 1 (n ana	lysed=193):	Group 2 (n=2	02):	Group 3 (n=211):	Group 4 (n=194):			
	Placebo + insulin ± OAD		2.5 mg dapag	liflozin + insulin ± OAD	5 mg dapa	agliflozin + insulin ± OAD	10 mg dapagliflozin + 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]	<mark>-0.79</mark>	-0.89 to -0.69 [graph]	-0.89	-0.99 to -0.79	<mark>-0.96</mark>	-1.06 to -0.86		
	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>	-1.12 to -0.9		
				P<0.0001 vs placebo		p<0.0001 vs placebo		p<0.0001 vs placek		
ΔWeight (kg)	wk 24: 0.43	0.05 to 0.81 [graph]	-0.92	-1.29 to -0.55	<mark>-1.0</mark>	-1.37 to -0.63	<mark>-1.61</mark>	-1.98 to -1.24		
0 (0,	wk 48: 0.82	0.29 to 1.35 [graph]	<mark>-0.96</mark>	-1.48 to -0.44	<mark>-1.0</mark>	-1.52 to -0.48	<mark>-1.61</mark>	-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	<mark>-1.10</mark>	-1.64 to -0.56. p NI		
(mmol/L)	wk 48: NR	•	<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 NI		
. , ,				p<0.0001 vs placebo		p<0.0001 vs placebo		p<0.0001 vs placek		
ΔSBP (mmHg)	wk 24: -3.56	-5.47 to -1.64	-4.21	-6.05 to -2.38, p NR	<mark>-5.93</mark>	-7.74 to -4.12, p NR	-6.66	-8.53 to -4.80, p NI		
- (0)	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	-4.09	-6.09 to -2.09, p NI		
	following recovery, capillary glucose <3.0mmol/L Other hypoglycaemia = suggestive criteria not meeting criteria for major or minor hypoglycaemia					ital Tract Infection lypotension lypoglycaemia (severe) Hypoglycaemia (mild)	Group 4 = n=	Group 3 = n=153 Group 4 = n=145 2 deaths in the 5 mg dapagliflozin gr		
						Hypoglycaemia (other)				
	Group 1 (n ana	alysed=193):	Group 2 (n=2	<mark>02):</mark>	Group 3 (n=211):	Group 4 (n=1	<mark>.94):</mark>		
	Placebo + insu	<mark>lin ± OAD</mark>	2.5 mg dapag	liflozin + insulin ± OAD	5 mg dapa	agliflozin + insulin ± OAD	10 mg dapag	liflozin + insulin ± OAD		
Specific events	UTI n=10, GTI	n=5	UTI n=16, GT	l n=13	UTI n=23,	GTI n=21	UTI n=20, GT	T n=21		
	HypoT n=2		HypoT n=5		HypoT n=!	5	HypoT n=3			
	HypoS n=2, Hy	<mark>rpoM n=99, HypoO n=11</mark>	HypoS n=3, H	ypoM n=118, HypoO n=19	HypoS n=2	<mark>2, HypoM n=113, HypoO n=2</mark> 4	HypoS n=3, HypoM n=99, HypoO n=21			
	Renal impairm	ent / failure n=3		ment / failure n=2		pairment / failure n=6	Renal impairment / failure n=4			
	Events leading	to discontinuation n=3	Events leadin	g to discontinuation n=2	Events lea	ading to discontinuation n=5		ng to discontinuation n=5		
	Nasopharyngit		Nasopharyng			yngitis n=35	Nasopharyng Nasopharyng			
	Headache n=1	<mark>5</mark>	Headache n=	<mark>11</mark>	<mark>Headache</mark>	e n=1 <mark>4</mark>	Headache n=	<mark>:5</mark>		
	Back pain n=11		Back pain n=1		<mark>Back pain</mark>		Back pain n=			
	Hypertension I		Hypertension		Hypertens 1		Hypertension Hypertension			
	Diarrhoea n=8		Diarrhoea n=		<mark>Diarrhoea</mark>		<mark>Diarrhoea n=</mark>			
		=3Peripheral oedema	Constipation		Constipati		Constipation			
	<mark>n=15</mark>		Peripheral oe			<mark>l oedema n=5</mark>	Peripheral of			
		act Infection n=12		ract Infection n=6		p. tract Infection n=8		tract Infection n=9		
	Arthralgia n=1	<u>1</u>	Arthralgia n=	4	Arthralgia	n=3	Arthralgia n=	:7		



Canagliflozin

	ggarwal N, Polidori D, Zhao inhibitor, as add-on to me					ose Fun	ding source: Janssen	Global Services
						or 3 vers vers	.T2 Inhibitor (50, 100 800 mg BD canaglifloz sus sitaglipitin + meti sus placebo + metfor	in) + metformin formin
	he safety, tolerability and e			e 2 diabetes who have	e inadequate glycaem	nic control on metform	min monotherapy	
Study quality	Medium – see quality ta		mation					
Study	Multi-centre: 85 (12 co							
particulars	Duration of interventio							
	Duration of run in: 4 we							
	Follow-up: 2 weeks pos	t-treatment						
	Design: 7-arm parallel g	roup RCT, double bl	ind, placebo controlled	t				
	Primary outcome: chan	ge from baseline in	HbA1c to week 12					
	Secondary outcomes:							
	 Change in FPG 							
	 Change in weight 							
	 Overnight glucose- 	to-creatinine ratio						
	 Change in proporti 	on of participants w	ith HbAc <7.0% and <6	5.5%				
		nction measured usi	ing HOMA2-%B					
	- Serum lipids							
	 Adverse events, lab 	ooratory assessment	ts, vital signs					
Participant	N: 451 analysed							
criteria	Inclusion criteria: partic							e (≥3 months) dose
	of ≥1500 mg/day; stable		25 (24 for Asians) to 45	5 kg/m²; serum creatir	nine <1.5mg/dl for me	en and <1.4mg/dl for	women	
	Exclusion criteria: not s	'						
Interventions	Intervention 1: placebo	· · ·						
	Intervention 2: canaglif							
	Intervention 3: canaglif	-						
	Intervention 4: canaglif	•						
	Intervention 5: canaglif	lozin 300 mg OD + m						
	Intervention 6: canaglif	lozin 300 mg BD + m						
	Intervention 6: canaglift Intervention 7: sitaglipt	lozin 300 mg BD + m in (sita) 100 mg OD	+ metformin					
	Intervention 6: canaglift Intervention 7: sitaglipt OAD schedule: metform	lozin 300 mg BD + m in (sita) 100 mg OD nin mean dose 1890	+ metformin SD479 mg/day					
	Intervention 6: canaglift Intervention 7: sitaglipt	lozin 300 mg BD + m in (sita) 100 mg OD nin mean dose 1890 itment screening ph	+ metformin SD479 mg/day ase					
Participant	Intervention 6: canaglift Intervention 7: sitaglipt OAD schedule: metform	lozin 300 mg BD + m in (sita) 100 mg OD nin mean dose 1890 ttment screening ph Group 1 pla +	+ metformin SD479 mg/day ase Group 2 cana	Group 3 cana	Group 4 cana	Group 5 cana	Group 6 cana	Group 7 sita
Participant baseline data	Intervention 6: canaglift Intervention 7: sitaglipt OAD schedule: metform	lozin 300 mg BD + m in (sita) 100 mg OD nin mean dose 1890 itment screening ph	+ metformin SD479 mg/day ase Group 2 cana 50 mg OD + met	100 mg OD + met	200 mg OD + met	300 mg OD + met	300 mg BD + met	100 mg OD + met
•	Intervention 6: canaglifi Intervention 7: sitaglipt OAD schedule: metform Lead in period: pre-trea	lozin 300 mg BD + m in (sita) 100 mg OD nin mean dose 1890 ttment screening ph Group 1 pla + met (n=65)	+ metformin SD479 mg/day ase Group 2 cana 50 mg OD + met (n=64)	100 mg OD + met (n=64)	200 mg OD + met (n=65)	300 mg OD + met (n=64)	300 mg BD + met (n=64)	100 mg OD + met (n=65)
•	Intervention 6: canaglift Intervention 7: sitaglipt OAD schedule: metform	lozin 300 mg BD + m in (sita) 100 mg OD nin mean dose 1890 ttment screening ph Group 1 pla +	+ metformin SD479 mg/day ase Group 2 cana 50 mg OD + met	100 mg OD + met	200 mg OD + met	300 mg OD + met	300 mg BD + met	100 mg OD + met

	Dag (1 / 2)	20.6.604.6	24.7	CDAC	24 7 60	- 0	24.4505.2		24.6	CD 4 0	24.0 CDF 2	24.6.605.0
	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 9	D12	128 SD13	129 SD13
Outcome (chang	ge from baseline at stu	<u> </u>		1				1				
	Group 1 pla + met	Group 2 cana 5	0 mg OD	Group 3		Group 4		Group 5			iroup 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 า=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	-(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 pla	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		vs placebo		vs placebo	p<0.001			<0.001 vs placebo	p NR
ΔSBP (mmHg)	-1.3 SE1.5	-0.9 SE1.7, p NR		_	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	-71-		-71		- / -		, _F	7,
	ent: adverse event rep	orts (Medical Dictiona	rv for Reg	ulatory Act	tivities), vital si	gns. physic	cal examinatio	ns. labora	torv a	ssessments	. self-administered va	ginal swabs
,		ia (HypoM) = symptor	, ,		neral events –	0 , , ,					e or more adverse ev	•
	capillary glucose <3.5				= Urinary Trac			, a		Group 1 = r		
		n ia (HypoS) = sympton	natic eniso		= Genital Trac					Group 2 = r		
		istance with following			o = Hypoglyca					Group 3 = r		
	capillary glucose <3.0	•	, recovery,	, , ,	oT = AEs sugge		notension			Group 4 = r		
	. , ,	a (HypoO) = symptom	s hut	,,	71233466	estive of m	poterision			Group 5 = r		
	without measuremen		15, Dut							Group 6 = r		
	without measuremen	in commining								Group 7 = r		
		Group 1 pla (n=65)	Group 2	cana	Group 3 car	na	Group 4 cana	6	roun	5 cana	Group 6 cana	Group 7 sita
		Gloup I pla (II-05)	50 mg O		100 mg OD		200 mg OD (n			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	3 OD (11-04)	n=3	n=1
Events	GTI	n=4 n=1	n=5		n=4		n=2	4	=2 =2		n=4	n=1
ragii(2	Symptomatic Hypo	n=1	n=0		n=4 n=1		n=4		=0		n=2	n=3
	, , , ,,	n=1 n=1	n=0 n=0		n=1 n=4		n=4 n=3		=0 =1		n=2 n=1	n=3 n=1
	HyopoT AEs leading to	n=1 n=2	n=0 n=1		n=4 n=3				=1 =2		n=1 n=2	n=0
		11-2	11=1		11=5		n=1	l n	-2		11=2	II=U
	discontinuation				<u> </u>		2					1
	Headache	n=2	n=1		n=5		n=2		=3		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.											

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





47

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



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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^2) for each meta-analysis.	N/A
o.			<u> </u>	

		Page 1 of 2	Demonstra
Section/topic	#	Checklist item	Reported on page
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	tables
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	tables
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1



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



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.	
autiois.	
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	
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.	
4) 71	
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	
	<u> </u>

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. 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.

Safety added. We have added "randomised controlled"
We have added "randomised controlled"
Figures for HbA1c changes added to Abstract. No change to "good quality" – it's a standard expression in systematic reviews.
Text on safety added to Abstract.
We don't think the use of bullets is excessive but will amend it if the editor wishes.
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.
Ne T VhN Valrph

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

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

sentence on literature search results. Would remove subheaders of	retained.
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.	
18) Would change figure 2 header to change in	Done
a1c by dapagliflozin dose.	
and the programme of the state	
19) If able, would be useful to have standard	Some figures removed
error bars in figures 2 through 5	
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 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 was list COLT2 to biblious	Daing based in the LUC was doubt to a live to
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	

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

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

inclusion criteria.	
The results of this systematic review have been presented in graphical format, with data points from all included studies plotted together. In this format it is difficult to interpret the data, though the authors have attempted to do this through narrative and overall statements. The authors state that a meta-analysis was not conducted because of the small number and heterogeneity of the trials. As 5 trials have been included in the review, and each of these report outcomes which can be compared, a meta-analysis could be conducted. The authors throughout the paper make summary statements about the results, however the method of analysis used by the investigators is not appropriate to draw these conclusions. A meta-analysis should be conducted and would substantially improve the	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
paper.	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	Figures were as calculated in original studies.
median? How was this calculation perfomed and which statistical package was used to get to this value? This value should be obtained using meta-analysis.	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.

	T
optimum dosage of 10-20mg.	
The presentation of the results in this review	We remain convinced that a meta-analysis would
needs to be revised.	not be appropriate.
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.	

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