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Systematic Review and Network Meta-analysis to Compare Dapagliflozin with other Diabetes Medications in Combination with Metformin for Adults with Type 2 Diabetes

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Abstract

Objective: A network meta-analysis (NMA) update was undertaken to evaluate the sodium glucose co-transporter-2 (SGLT-2) inhibitor, dapagliflozin, versus other antidiabetes medications as add-on to metformin. This update allowed inclusion of a new drug class (glucagon-like peptide-1 [GLP-1] analogues), a new time point (24-weeks) and covariate analysis.

Methods: The systematic review identified randomised controlled trials involving patients with type-2 diabetes mellitus (T2DM) inadequately controlled on metformin. Comparators included dipeptidyl peptidase-4 inhibitors (DPP-4i), thiazolidinediones (TZDs), GLP-1s, sulfonylureas (SUs) and dapagliflozin. Bayesian NMA was conducted at 24- and 52-weeks for mean change in HbA1c, systolic blood pressure (SBP), weight, and proportion of patients experiencing hypoglycaemia.

Results: The systematic review identified 2247 articles, of which 16were eligible for inclusion. Combined with 19 studies frompre-2011 analysis, a total of 19 and 8 studies were included in the 24-week and 52-week NMA, respectively. There were no significant differences in HbA1c or SBP between dapagliflozin and other classes, including GLP-1s, at either time point. Significant results were seen for weight loss by 24-weeks for dapagliflozin versusDPP-4i (-2.24 kg [95% CI -3.25,-1.24]) and TZDs (-4.65 kg [-5.89,-3.45]), and at 52-weeks versus SUs, DPP-4i and TZDs. Dapagliflozin also resulted in significantly lower hypoglycaemia risk versus SU (OR: 0.05 [0.01,0.19]) over 52-weeks.

Conclusions: This NMA update supports previous findings that effects on HbA1c are similar between drug classes and that dapagliflozin plus metformin offers superior weight control for T2DM patients compared with many other agents. The wider evidence base compared to previous analysis increases the confidence in the results.

Keywords: Diabetes; Dapagliflozin; Systematic review; Network meta-analysis

Introduction

Type 2 diabetes mellitus (T2DM) is increasingly prevalent worldwide with at least 285 million people currently affected [1]. This figure is predicted to rise to 438 million by 2030.T2DM is associated with the growing rate of obesity and the economic burden is estimated to be responsible for 12% of healthcare expenditure globally [2], with around 80% of the costs estimated to come from the treatment and management of avoidable diabetes-related complications [3]. Reducing the burden of T2DM can therefore be achieved through effective management of the disease.

International guidelines currently recommend lifestyle modification followed by metformin monotherapy as a first line treatment [4]. However, many patients will require additional therapeutics to maintain glycaemic control as the disease progresses. Currently available treatment classes licensed for add-on to metformin in T2DM include dipeptidyl peptidase 4 inhibitors (DPP-4i), glucagon-like peptide 1 (GLP-1) analogues, thiazolidinediones (TZDs), sulfonylureas (SUs) and a new class of agent, sodium glucose co-transporter 2 (SGLT-2) inhibitors. There are many factors to consider when assessing the suitability of available agents, such as the HbA1c-lowering efficacy and safety profile, as well as the cost of drug acquisition and managing related side effects. The side effects of each treatment strategy, including the incidence of hypoglycaemia and the effect on patient weight, are key considerations as they can have a significant impact on continuation rates and patient quality of life [5,6].

Dapagliflozin is the first-in-class SGLT-2 inhibit or approved by the European Medicines Agency (EMA), and has recently gained approval

by the Food and Drug Administration (FDA).The efficacy, safety and tolerability of dapagliflozin as an add-on therapy to metformin has been studied in previous randomised controlled trials (RCTs) compared to both placebo [7] and to a SU [8]. It demonstrates a novel treatment effect through an insulin independent mechanism of action associated with weight loss. Whereas DPP-4i, GLP-1 analogues and SUs stimulate insulin production from pancreatic beta cells and TZDs target specific nuclear receptors leading to increased insulin sensitivity of liver, fat and skeletal muscle cells, dapagliflozin inhibits glucose reabsorption in the kidneys. Dapagliflozin therefore acts independently of insulin secretion or action, and results in calorific loss by increasing the glucose concentration in urine.

A 52-week NMA assessing the relative efficacy of dapagliflozin, DPP-4is, TZDs and SUs all in combination with metformin has previously been conducted [9]. This analysis showed that compared to DPP-4i, TZDs and SUs, dapagliflozin offered similar HbA1ccontrol after one year, with a similar or reduced risk of hypoglycaemia and a reduction in weight. An updated analysis was required to provide a more comprehensive assessment of available treatments by incorporating additional trials published since the last review, and in particular, to include the newly licensed GLP-1 class. The NMA presented here also aimed to provide additional results at both 24-weeks and 52-weeks, and to include an additional analysis of change in systolic blood pressure (SBP).

Materials and Methods

The study methodology comprised two components: a systematic review of the literature and an indirect comparison of eligible randomised controlled trials (RCTs), including a Bayesian NMA.

Systematic review

As per the original systematic review [9], this study was conducted to identify RCTs of antidiabetes agents licensed in the European Union (EU) for add-on to metformin, based on a pre-defined review protocol. Outcomes of interest were selected based on clinical priorities and data availability, and included mean change in HbA1c from baseline, mean change in SBP from baseline, mean change in weight from baseline, and the proportion of subjects experiencing at least one episode of hypoglycaemia.

Eligible studies for inclusion in the review were RCTs with a minimum follow up of 18 weeks, conducted in adults with T2DM inadequately controlled by metformin alone. To be included in the meta-analysis, studies were required to report outcomes of interest at 24-weeks± 6 weeks (± 8 weeks in sensitivity analysis) or 52-weeks ± 6 weeks. Inclusion and exclusion criteria for this systematic review were developed to ensure that trials were sufficiently similar to be pooled in the meta-analysis (Table 1).

Inclusion criteria	Description
Population	Adults (≥18 years) with T2DM Inadequate glycaemic control on metformin monotherapy
Interventions	Pharmacological therapies that would be added to metformin in clinical practice when metformin does not provide adequate glycaemic control
Comparators	Active arms: Dual therapies of interest, namely drugs licensed in the EU in combination with metformin, investigated at a licensed dose and where used in clinical practice
Outcomes	To be included in the metaanalysis, studies needed to report at least one of the primary endpoints of interest at 24 ± 6 weeks (± 8 weeks in sensitivity analysis) or 52 ± 6 weeks: mean change in HbA1c from baseline; mean change in systolic blood pressure from baseline; mean change in weight from baseline; proportion (number) of patients experiencing at least one hypoglycaemic episode
Study design	Prospective, randomised, placebo or activecontrolled trials If crossover design, then results reported prior to the crossover period can be used in the metaanalysis Minimum followup of 18 weeks to be included in the base case meta-analysis (i.e. 24-weeks ± 6 weeks; ± 8 weeks for sensitivity analysis)
Publications	Full-text publications, except for abstracts published in 2012-2013 (for results from recently completed trials) Full-text available in English
Exclusions	Results from uncontrolled open label extensions of RCTs Study populations with moderate to severe renal impairment
EU: European Union; HbA1c: Glycated Haemoglobin; RCT: Randomised Controlled Trial; T2DM: Type 2 Diabetes Mellitus	

Table 1: Inclusion and exclusion criteria for the systematic review to identify clinical evidence for licensed antidiabetes agents as add-on to metformin

The dapagliflozin clinical trial design [7] was chosen as a benchmark as it concurs with EMA regulatory guidelines on assessing efficacy and safety for diabetes treatments [10]. These guidelines state that confirmatory studies should typically be 6 months in duration and the maintenance period, where the dose of the glucose-lowering agent is kept constant, should be sustained for at least 18 weeks, including a minimum 2-week titration period. As such, a 24-week time point with a maximum window of ± 6 weeks was chosen to allow for a pooled

analysis of short term endpoints to be conducted in adherence to the EMA guidelines. RCTs reporting outcomes at ± 8 weeks were included in a sensitivity analysis according to the pre-defined protocol.

Study arms were pooled by drug class to improve precision by increasing the amount of data available for each class-level comparison. An overview of the individual drugs within each class, along with the licensed dose ranges, is provided in Table 2. Alpha-glucosidase inhibitors were not considered, as they are not commonly used in the EU [11]. Likewise, insulin, as an add-on to metformin, was not included in the scope of this review as it was not considered to be a relevant comparator at this stage of the treatment pathway [12]. SUs were excluded from the 24-week analysis as their dose may be titrated for up to 18 weeks of therapy, which leads to varying effect sizes over this period. Therefore, it was considered that a comparison of SU trials at the 52-week time point would be more appropriate.

Class	Drug	EU indication	
		Dose (min)	Dose (max)
SGLT-2 inhibitors	Dapagliflozin	10 mg od	10 mg od
GLP-1 analogues	Exenatide	5 µgbd	10 µgbd
	Exenatide PR	2 mg once weekly	2 mg once weekly
	Liraglutide	0.6 mg od[a]	1.8 mg od
	Lixisenatide	10 µgod[b]	20 µg od
TZD	Pioglitazone	15 mg od[c,d]	45 mg od
SU	Glyburide/ Glibenclamide	5 mg od	15 mg od
	Glimepiride	1 mg od	6 mg od
	Glipizide	5 mg od	20 mg od[e]
	Gliclazide PR	30 mg od	120 mg od
DPP-4 inhibitors	Linagliptin	5 mg od	5 mg od
	Saxagliptin	5 mg od	5 mg od
	Sitagliptin	100 mg od	100 mg od
	Vildagliptin	50 mg bd	50 mg bd
Metformin	Metformin	500 mg od	3000 mg od[f]
	Metformin PR	500 mg od	2000 mg od

SGLT-2: Sodium Glucose Transporter2; GLP-1: Glucagonlike Peptide1; TZD, Thiazolidinedione; SU: Sulfonylurea; DPP-4i: Dipeptidyl Peptidase4 Inhibitors; od: once daily; bd: twice daily; PR: Prolonged Release

[a]initial dose, titrated to 1.2 mg; [b]starting dose for 14 days, titrated to 20 µg at day 15; [c]initial dose only, titrated to 30mg and 4 mg therapeutic dose; [d]initial dose only, titrated to 30 mg and 45 mg therapeutic dose; [e]above 15 mg to be divided doses; [f]divided doses

Table 2: EU licensed dosing for agents used as addon to metformin treatment

The original search strategy, conducted in May 2011 [9], was updated to address the recent approval of the GLP-1 analogues. Search dates were overlapped to ensure publications still in process in May 2011 were included in the results. The review was carried out using a structured search (Table S1) via the OVID platform of the following electronic databases: CENTRAL (2011 to 6th July 2013), Medline and Medline In-Process (2011 to 6th July 2013), and Embase (2011 to 8th July 2013). The conference proceedings for the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) were searched for relevant abstracts in 2012 and 2013 (where available), and the clinical trials registry (ClinicalTrials.gov) was hand-searched for unpublished trials. Each citation was initially screened based on the abstract and title, followed by a second-stage, full text review for relevant studies. Outcomes of interest were extracted from the eligible studies, with any disputes being resolved by a third party. Quality assessments of the included studies were conducted using the Cochrane Collaboration's tool for assessing risk of bias [13]. The impact of including studies where there were concerns over the quality of data reported was investigated through sensitivity analysis.

Meta-analyses

The network meta-analysis methodology used was as per the NICE Decision Support Unit recommendations for random and fixed-effect Bayesian NMA of continuous and dichotomous data [14]. Continuous outcomes were analysed by a normal model with identity link and dichotomous outcomes by a binomial model with log it link. The NMA was conducted on a modified intent-to-treat (mITT) basis where the mITT population was defined as the set of patients who were randomised and received at least one dose of study medication. The pooled summary measure for continuous endpoints was weighted mean differences (WMD) and odd ratios (OR) for binomial outcomes. For continuous endpoints both the mean and standard error were required for the NMA. Missing standard errors were calculated within WinBUGs by assuming that observed and unobserved values were exchangeable, and that sample variances followed a gamma distribution with a common standard deviation [15,16]. This allowed the NMA to make greater use of the available data.

Fixed-effect and random effects models were investigated at both 24- and 52-weeks. The models were fitted to the data via Bayesian Markov Chain Monte Carlo methods using WinBUGs. An estimate of how well the predicted values fitted the observed dataset was provided by the mean residual deviances (total residual deviance divided by number of data points), as well as the deviance information criteria (DIC) outputted by WinBUGs [14].

A covariate analysis explored the effect of potentially confounding baseline factors for the HbA1c endpoint [17]. Note that this meta-regression adjusts the treatment effects for differences between trials as opposed to differences at a patient level. Covariates were analysed using a continuous, study arm level variable, assuming the same effect across all treatments. The coefficient represents the mean change at follow up versus baseline for each unit increase in the study arm level covariate at baseline. To maximise the data, missing baseline values were calculated assuming observed and unobserved values were exchangeable [18]. Previous meta-analyses have shown that there is a correlation between the average baseline HbA1c and change in HbA1c over follow-up [19] and it is known that glycaemic control is harder to achieve in overweight or obese patients [20]. Patient age was also considered to be a potential effect modifier in itself. Sufficient data were available to conduct a covariate analysis for the 24-week HbA1c network, including three covariates aggregated at the study arm-level: average baseline HbA1c, average baseline weight and average patient

age. For the 52-week HbA1c network, data were available to carry out a covariate analysis using average baseline HbA1c as a single covariate.

Direct meta-analysis was also conducted, where the random-effects model used the method of Der Simonian & Laird, with the estimate of heterogeneity being taken from the fixed-effect Mantel Haenszel or inverse variance model [21]. Indirect comparisons were then made using the Bucher method [22] and employing the pooled effects produced from the direct meta-analysis. The direct and Bucher indirect meta-analysis were conducted to validate the NMA. Results of the HbA1c direct meta-analyses are presented as forest plots in the supplementary information (Figure S2 and Figure S3).

Results

Systematic review search results

The updated OVID database search retrieved 2224 citations published between 2011 and July 2013. A further 19 abstracts were retrieved from 2012 conference proceedings, and four studies were identified from the clinical trial registry and hand searching (Figure 1). Of the 2247 citations, 379 duplicates were removed and 1821 citations were excluded during the title and abstract review stage. The full-text of 47 citations was reviewed, with 16 of these eligible for inclusion in the updated NMA. These studies were merged with the results of the previous review [9], giving a total of 35 distinct randomised controlled studies [7,8,23-56]. Four abstracts that had been included in the previous analysis were replaced by full-text publications. In total,19 studies were included in the base case analysis at 24-weeks ± 6 weeks [7,23,25-41] (Table S2) and a further 4 were eligible for the sensitivity analysis due to timeframe (± 8 weeks) and quality issues (Table S4). Of the 15 studies reporting data at the 52-week time point, 8 were included in the base case analysis [8,42-48] (Table S3) with the remaining 7 assessed in the sensitivity analysis for the same reasons (timeframe and quality issues) (Table S4). Two included studies presented outcomes at both 24- and 52-weeks [23,24] and one study reported data from two citations [23,57].

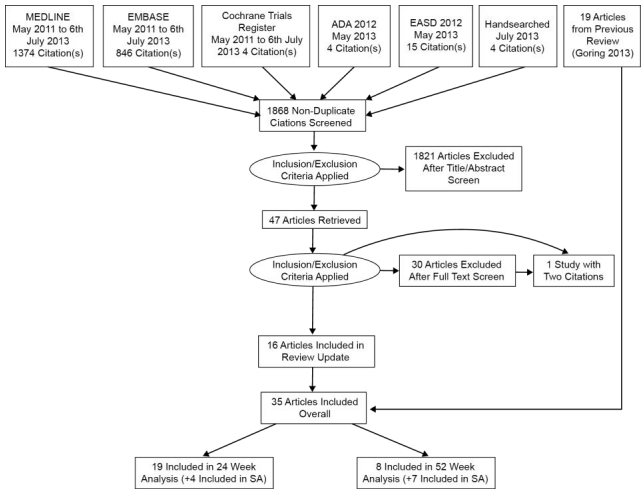

Figure 1: Flow diagram of study selection

SA: sensitivity Analysis

The included trials were all similar in terms of baseline characteristics and entry criteria. In the 24-week base case analysis, the average HbA1c at baseline across study arms was 8.15, weight was 86.18 kg, age was 54.9 years, the duration of diabetes was 6.12 years and 46.8% of patients were female. For the 52-week base case analysis, the average HbA1c at baseline across the study arms was 7.98, weight was 89.53 kg, age was 57.5 years, the duration of diabetes was 6.02 years and 45.8% of the patients were female. In both analyses, most studies reported background metformin at a stable dose of at least 1.5 g per day. The studies included in the base case analysis were determined to be of high quality using the Cochrane Collaboration's tool for assessing risk of bias (Figure S1).

Network overview

There were two evidence networks: a 24-week network with placebo as the reference treatment (Figure 2A) and a 52-week network with SU as the reference treatment (Figure 2B). The figure portrays the respective HbA1c network.

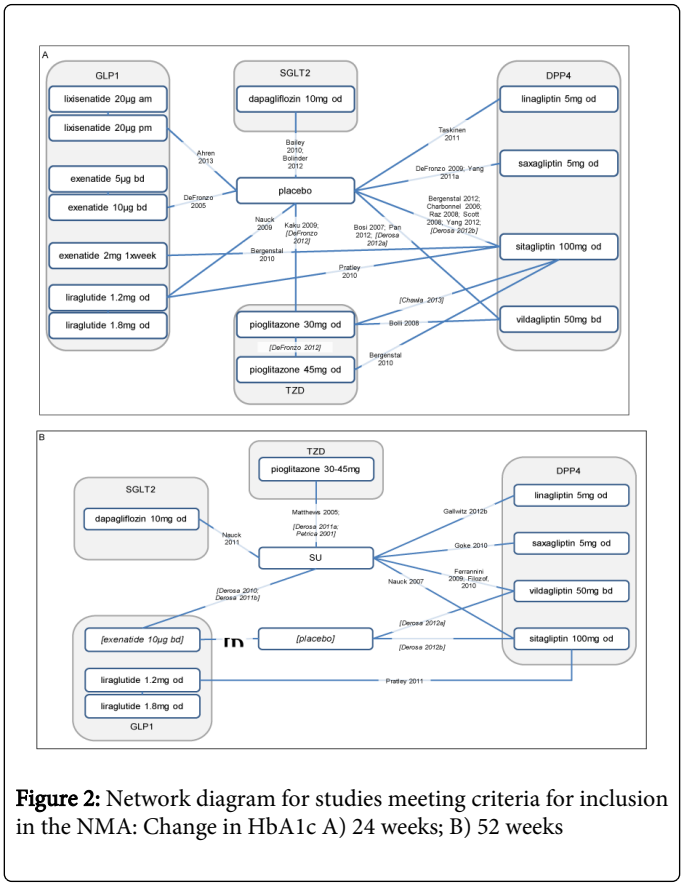

Figure 2: Network diagram for studies meeting criteria for inclusion in the NMA: Change in HbA1c A) 24 weeks; B) 52 weeks

HbA1c outcome

Four models were tested as part of the NMA for HbA1c change from baseline for both time points; both fixed-effect and random-effects models, with and without the covariates. For the HbA1c endpoint in the 24-week NMA, the coefficients for average weight and average age were not found to be significant.

The coefficient β(HbA1c) was significant for the fixed-effect model (-0.29; credible interval (CrI) -0.49, -0.09), and borderline significant for the random-effects model (-0.31; CrI -0.71, 0.10).The random-

effects model produced the best fit to the data. As such, the random-effects covariate model was preferred and the indicated trend towards a larger reduction in HbA1c reported in trials with a higher average Hba1c at baseline is consistent with clinical observation. This model resulted in a significant HbA1c reduction compared to baseline of -0.68 (CrI -1.15, -0.22) over 24-weeks for dapagliflozin; significant reductions were also seen for all other classes of compounds (Table 3).

All classes of antidiabetes drugs resulted in significantly lower absolute value of HbA1c at follow-up compared to placebo. There were no statistically significant differences in HbA1c between dapagliflozin and GLP-1, DPP-4i, or TZD using the random effects covariate model (Table 3). The difference in HbA1c between dapagliflozin and GLP-1 was statistically significant using the random-effects model without covariates, with GLP-1 demonstrating increased efficacy for this outcome (Table 3).

24-week NMA	RE NMA	RE NMA with 3 Covariates†
Difference from baseline		
Dapagliflozin	-0.49 (-0.87, -0.11)*	-0.68 (-1.15, -0.22)*
GLP-1	-0.99 (-1.24, -0.74)*	-0.98 (-1.24, -0.73)*
DPP-4i	-0.74 (-0.94, -0.56)*	-0.75 (-0.96, -0.55)*
TZD	-0.89 (-1.23, -0.56)*	-0.94 (-1.31, -0.58)*
Difference v placebo		
Dapagliflozin	-0.41 (-0.77, -0.04)*	-0.60 (-1.06, -0.16)*
GLP-1	-0.91 (-1.13, -0.69)*	-0.90 (-1.13, -0.67)*
DPP-4i	-0.66 (-0.82, -0.51)*	-0.67 (-0.84, -0.50)*
TZD	-0.81 (-1.13, -0.50)*	-0.86 (-1.21, -0.52)*
Difference headtohead		
Dapagliflozin v GLP-1	0.50 (0.08, 0.93)*	0.30 (-0.21, 0.81)
Dapagliflozin v DPP-4i	0.26 (-0.14, 0.65)	0.07 (-0.42, 0.55)
Dapagliflozin v TZD	0.40 (-0.08, 0.89)	0.25 (-0.30, 0.81)
52-week NMA	RE NMA	RE NMA with 1 Covariate§
Difference from baseline		
Dapagliflozin	-0.67 (-0.98, -0.36)*	-0.68 (-1.11, -0.25)*
GLP-1	-1.08 (-1.42, -0.75)*	-1.10 (-1.53, -0.67)*
DPP-4i	-0.56 (-0.74, -0.39)*	-0.58 (-0.81, -0.35)*
TZD	-0.65 (-0.99, -0.32)*	-0.62 (-1.16, -0.08)*
SU	-0.67 (-0.79, -0.54)*	-0.67 (-0.80, -0.55)*
Difference v SU		
Dapagliflozin	0.00 (-0.29, 0.29)	-0.01 (-0.43, 0.41)
GLP-1	-0.41 (-0.73, -0.10)*	-0.43 (-0.85, -0.01)*
DPP-4i	0.11 (-0.03, 0.23)	0.09 (-0.11, 0.29)
TZD	0.02 (-0.29, 0.33)	0.05 (-0.48, 0.58)
Difference headtohead		
Dapagliflozin v GLP-1	0.41 (-0.01, 0.84)	0.42 (-0.14, 0.99)
Dapagliflozin v DPP-4i	-0.11 (-0.42, 0.22)	-0.11 (-0.53, 0.34)
Dapagliflozin v TZD	-0.02 (-0.45, 0.40)	-0.06 (-0.80, 0.68)

*statistically significant result based on 95% credible interval;

†3 covariates: arm level HbA1c, weight and age at baseline

§1 covariate: arm level HbA1c at baseline

(95% credible interval); DPP-4i: Dipeptidyl Peptidase4 Inhibitor; FE: FixedEffect; GLP-1: GlucagonLike Peptide1; NMA: Network MetaAnalysis; RE: Random-Effects; SGLT-2: Sodium Glucose Transporter2; SU: Sulfonylurea; TZD: Thiazolidinediones

Table 3: Relative effect size by class for HbA1c weighted mean difference from network meta-analysis of trials enrolling patients with T2DM inadequately controlled on metformin monotherapy (analysis with the best model fit is highlighted in bold).

In the 52-week covariate NMA for the HbA1c endpoint, the random-effects model was shown to fit the data better than the fixed-effect model, while the addition of covariates did not improve the model fit (Table 3). Additionally, the coefficient β (HbA1c) was shown not to be significant. As such, the random-effects model without covariates was preferred. No statistically significant differences in HbA1c were observed for the head to head comparisons, andGLP-1 analogues were the only class to demonstrate a statistically significant difference in HbA1c compared to SU at 52-weeks (Table 3).

Additonal outcomes – 24-week network

Two models (fixed-effect and random-effects) were used to compare the outcomes of SBP, weight, and the incidence of hypoglycaemia in the 24-week and 52-week analysis (Table 4). In all instances, the random-effects model fitted the data better. With respect to SBP, dapagliflozin was the only agent to be associated with a statistically significant change in SBP from baseline at 24-weeks. There were no significant differences in SBP between dapagliflozin and the other classes of antidiabetes drugs at 24-weeks. Dapagliflozin was shown to result in a statistically significant lower weight compared to placebo, DPP-4i and TZD at 24-weeks, with a reduction of -2.04 kg (-2.97, -1.12), -2.24 kg (-3.25, -1.24) and -4.65 kg (-5.89, -3.45), respectively. Although the comparison between dapagliflozin and GLP-1 resulted in a relative weight loss at 24-weeks for dapagliflozin (-0.61 kg [-1.69, 0.46]), this was not statistically significant in the random-effects model. The incidences of hypoglycaemic events were shown to be similar across all comparators in the 24-week NMA.

Additonal outcomes – 52-week network

The results were largely seen to extend to the 52-week time point (Table 4). Due to the lack of reporting across the 52-week trial data, an NMA for SBP was not carried out. Data based on the fixed-effect direct and Bucher indirect comparisons showed that dapagliflozin had a similar effect on SBP compared to GLP-1 and DPP-4i, and resulted in a significant reduction when compared to SU control (Table 4). Based on the random-effects NMA, dapagliflozin resulted in a substantial reduction in weight (-3.30 kg [-5.07, -1.53]) versus baseline. Statistically significant weight loss was also observed when compared

with SU, DPP-4i and TZD at 52-weeks, with reductions of -4.66 kg (-6.43, -2.90), -2.59 kg (-4.53, -0.66) and -4.76 kg (-7.28, -2.24), respectively. A weight change of -0.53 kg (-3.05, 2.00) was associated with dapagliflozin in comparison to GLP-1 at 52-weeks, although this difference was not significant. Dapagliflozin was associated with a numerically lower risk of developing hypoglycaemia with respect to all drug classes at 52-weeks, and this reduction was significant when compared to SU (OR 0.05 [0.01, 0.19]).

Comparison	24 Week RE NMA		52 Week RE NMA	
SBP				
		RE NMA		**FE Direct [Indirect]**
Difference v baseline	24 week	SBP (mmHg)	52 Week	SBP (mmHg)
Dapagliflozin	Baseline	-5.23 (-9.58, -0.89)*	Baseline	-
GLP-1	Baseline	-3.05 (-7.04, 1.01)	Baseline	-
DPP-4i	Baseline	-1.99 (-5.77, 1.90)	Baseline	-
TZD	Baseline	-2.52 (-7.67, 2.86)	Baseline	-
Difference v control				
Dapagliflozin	Placebo	-3.76 (-7.15, -0.41)*	SU	-5.1 (CI: -8.27, -1.93)**
GLP-1	Placebo	-1.59 (-4.44, 1.42)	SU	-
DPP-4i	Placebo	-0.54 (-3.09, 2.25)	SU	-2.9 (CI: -4.93, -0.87)**
TZD	Placebo	-1.06 (-5.39, 3.56)	SU	-
Difference headtohead				
Dapagliflozin	GLP-1	-2.16 (-6.73, 2.19)	GLP-1	[-1.48 (CI: -6.01, 3.05)]
Dapagliflozin	DPP-4i	-3.22 (-7.65, 0.93)	DPP-4i	[-2.2 (CI: -5.97, 1.57)]
Dapagliflozin	TZD	-2.69 (-8.52, 2.72)	TZD	-
Weight (kg)				
		RE NMA		**RE NMA**
Difference v baseline	24 week	Weight (kg)	52 Week	Weight (kg)
Dapagliflozin	Baseline	-2.89 (-3.86, -1.93)*	Baseline	-3.30 (-5.07, -1.53)*
GLP-1	Baseline	-2.28 (-2.90, -1.66)*	Baseline	-2.77 (-4.59, -0.96)*
DPP-4i	Baseline	-0.65 (-1.13, -0.17)*	Baseline	-0.71 (-1.52, 0.10)
TZD	Baseline	1.76 (0.93, 2.62)*	Baseline	1.46 (-0.36, 3.27)
SU	Baseline	NA	Baseline	1.36 (1.19, 1.54)*
Difference v control				
Dapagliflozin	Placebo	-2.04 (-2.97, -1.12)*	SU	-4.66 (-6.43, -2.90)*
GLP-1	Placebo	-1.43 (-1.98, -0.88)*	SU	-4.13 (-5.94, -2.32)*
DPP-4i	Placebo	0.20 (-0.19, 0.59)	SU	-2.07 (-2.87, -1.28)*
TZD	Placebo	2.61 (1.83, 3.42)*	SU	0.10 (-1.72, 1.90)
Difference headtohead				
Dapagliflozin	GLP-1	-0.61 (-1.69, 0.46)	GLP-1	-0.53 (-3.05, 2.00)
Dapagliflozin	DPP-4i	-2.24 (-3.25, -1.24)*	DPP-4i	-2.59 (-4.53, -0.66)*
Dapagliflozin	TZD	-4.65 (-5.89, -3.45)*	TZD	-4.76 (-7.28, -2.24)*
Patients with hypoglycaemia				

		RE NMA		**RE NMA**
OR v control	24 week	Hypoglycaemia	52 Week	Hypoglycaemia
Dapagliflozin	Placebo	0.99 (0.25, 3.89)	SU	0.05 (0.01, 0.19)*
GLP-1	Placebo	1.24 (0.58, 2.84)	SU	-
DPP-4i	Placebo	0.92 (0.50, 1.74)	SU	0.09 (0.05, 0.17)*
TZD	Placebo	0.39 (0.04, 2.32)	SU	0.09 (0.02, 0.41)*
OR headtohead				
Dapagliflozin	GLP-1	0.79 (0.16, 3.82)	GLP-1	-
Dapagliflozin	DPP-4i	1.08 (0.24, 4.74)	DPP-4i	0.57 (0.14, 2.56)
Dapagliflozin	TZD	2.56 (0.26, 33.50)	TZD	0.57 (0.08, 4.81)

(95% credible interval); *statistically significant result based on 95% credible interval; **statistically significant p<0.05; CI: Confidence Interval; DPP-4i: Dipeptidyl Peptidase4 Inhibitor; FE: FixedEffect; GLP-1: GlucagonLike Peptide1; NMA: Network MetaAnalysis; RE: Random-Effects; SGLT-2: Sodium Glucose Transporter2; SU: Sulfonylurea; TZD: Thiazolidinediones

Table 4: 24- and 52-Week random effects network meta-analysis results for Weight and SBP weighted mean difference, and hypoglycaemia odds ratio

Sensitivity analysis

Sensitivity analyses based on quality issues and timeframe (± 8 weeks) were conducted for both the 24-week and 52-week analyses (Table S 4). Comparing the sensitivity analysis with the base case demonstrated little difference between results.

Discussion

The conclusions of the current analysis largely agree with the previous NMA, in that at 52-weeks non-SU agents showed a significantly lower risk of hypoglycaemia relative to SUs, and dapagliflozin was associated with a significant decrease in weight compared to DPP-4i and SUs [9]. Whereas in the previous analysis only six studies had been available for inclusion in the base case NMA, the current analysis included 19 studies in the 24-week base case and 8 studies in the 52-week base case. The outcomes presented here therefore have a much wider evidence base than the previously reported analysis, which increases the confidence in the results. The newly included GLP-1 class were found to be associated with a significant effect on HbA1c at both 24-weeks and 52-weeks versus placebo and SUs, respectively. However, unlike dapagliflozin, GLP-1 analogues were not associated with a significant effect on SBP compared to placebo at 24-weeks.

Strengths and limitations

The comprehensive nature of the systematic review and the relatively large number of included studies means that this analysis can reliably be used to answer clinically meaningful questions. Not only were glycaemic control and SBP investigated, but also the secondary outcome of weight, which has been shown to be highly important to patients [58]. Favourable outcomes on these commonly documented side effects could have a significant impact on patient quality of life, highlighting the importance of dapagliflozin's association with improved weight outcomes versus placebo/SU, DPP4i and TZD at both 24 and 52-weeks, and significantly less hypoglycaemia versus SU. On a similar note, one of the most critical factors that reduces adherence to therapy is the associated side-effects or lack of tolerability associated with therapeutics. Therefore, if tolerability is improved (i.e. reduced incidence of hypoglycaemic events, weight decrease), this should lead to improved treatment satisfaction, and in turn, result in better adherence to therapy, increased likelihood of target attainment and better outcomes for patients [59]. The relative effectiveness results presented here could also be used to inform a health economic model so that the clinical benefits of each antidiabetes agent in combination with metformin can be balanced against the economic consequences. However, agents used as add-on to metformin make up only one part of the T2DM treatment pathway. Additional reviews and NMAs are required to compare the efficacy and safety of dapagliflozin and other therapies as monotherapies or in combination with other agents such as SU [60].

A general limitation of meta-analyses is the underlying assumption that trials and outcomes are sufficiently similar to allow the accurate comparison of data. The review was focussed to a specific part of the treatment pathway to minimise the influence of non-comparable populations, although moderate between-study heterogeneity did exist, indicating that some unexplained differences between study designs or population characteristics had not been accounted for. Covariate analyses were undertaken to control for these confounding factors; specifically, the baseline HbA1c, age and weight were considered. The coefficient β(HbA1c) for the HbA1c endpoint was found to be significant for the 24-week fixed-effect NMA and borderline significant for the 24-week random-effects NMA. This is consistent with clinical observations that suggest there is a trend towards a larger reduction in HbA1c given a higher HbA1c at baseline [19]. The other coefficients (weight and age) in the 24-week analysis were not found to be significant.

Variation in the definition of hypoglycaemia may also be a source of heterogeneity between the included trials. In most cases, hypoglycaemia was defined as a major or minor symptomatic event, and variability between trials generally resulted from whether a finger stick test was used for confirmation. However, in some instances, asymptomatic hypoglycaemia was also recorded through finger stick tests alone. Another potential source of heterogeneity is the differences

in follow-up times across studies. A 24-week time point was chosen since most applicable studies were of this duration, and a ± 6 week window was selected to account for variation. The small nature of the window ensured that any impact on the study outcomes associated with time would be limited. Studies reporting outcomes at an extended period of 24±8 weeks were included in the sensitivity analysis, along with studies that had been ruled out due to quality issues. In both the 24-week and 52-week analyses there was no discernible difference between the base case and sensitivity analysis results. The sensitivity analyses confirmed the results are both robust and largely insensitive to small changes in the review scope. However, in the 24-week base case, the change in HbA1c was slightly less for GLP-1s, DPP-4i and TZDs. This suggests that the base case analysis produces a more conservative estimate for dapagliflozin compared to the other treatment options. At the time of analysis, dapagliflozin was the sole member of the SGLT-2 inhibitor class that was licensed and therefore included in the NMA. Since the systematic review update was conducted, another SGLT-2 inhibitor, canagliflozin, has received a marketing authorisation for add-on to metformin in T2DM.However, a recent study has shown that the data presented in this NMA are in-line with class level observations for SGLT-2 inhibitors, and that dapagliflozin remains responsible for the majority of publications associated with this class [25]. As such, it is reasonable to consider it a suitable class representative at the current time.

Conclusion

The first-in class SGLT-2 inhibitor, dapagliflozin, was compared with GLP-1 analogues, TZDs, DPP-4i and SUs as an add-on to metformin, in patients with inadequately controlled glycaemic levels on metformin monotherapy. Lowering of HbA1c was comparable across all classes. However, dapagliflozin offered superior weight control when compared with DPP-4i, TZDs and SUs, which is due to its different mechanism of action whereby dapagliflozin acts by an insulin independent method to reduce glucose reabsorption in the kidney, resulting in calorific loss. Additionally, dapagliflozin plus metformin was also associated with a significantly reduced risk of hypoglycaemia, over 52-weeks, in comparison to SU plus metformin. Although a sufficient total number of trials were included in the systematic review, there remains a general limitation as to the availability of data across comparative classes. For instance, the GLP1 v SU results were indirect (via GLP1 v DPP4i then DPP4i v SU trials) and not confirmed in head-to-head trials.Therefore, it could be of interest to update the current analyses once new clinical data becomes available for dapagliflozin or alternative classes.

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