

Liraglutide Versus SGLT-2 Inhibitors in People with Type 2 Diabetes: A Network Meta-Analysis

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ABSTRACT

Introduction: For people with type 2 diabetes (T2DM) inadequately controlled with oral antidiabetic drugs (OADs), evidence from both randomized controlled trials (RCTs) and real-world studies has demonstrated that treatment intensification with liraglutide offers effective glycemic control, weight reduction, and a lower risk of hypoglycemia compared to treatment intensification with insulin or additional OADs. Sodium glucose cotransporter 2 (SGLT-2) inhibitors are a new class of OADs that have also been shown to be effective in T2DM patients inadequately controlled with OADs.

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Currently there are no head-to-head RCTs comparing these to liraglutide.

Methods: We aimed to evaluate the relative efficacy, using network meta-analysis (NMA), of treatment intensification with liraglutide and SGLT-2 inhibitors people with T2DM who have been treated with metformin (alone or in combination with SU, DPP-4, and TZD). We performed a systematic literature review to identify relevant RCTs comparing liraglutide (1.2 and 1.8 mg), canagliflozin (100 and 300 mg), empagliflozin (10 and 25 mg), or dapagliflozin (5 and 10 mg) to placebo. To strengthen the indirect evidence base, we also included non-placebo RCTs where sitagliptin (100 mg) was the active comparator. Bayesian NMA was performed on the following outcomes to assess the relative efficacy and safety of interventions: reduction (change) in HbA1c, weight, and fasting plasma glucose (FPG) as well as proportion reaching target HbA1c (<7%), and risk of hypoglycemia. Doses for each intervention were considered separately.

Results: A total of 16 RCTs were identified. All trials were similar with respect to important baseline characteristics and study design. Both doses of liraglutide were generally statistically

significantly superior to the SGLT-2s with respect to change from baseline in HbA1c and FPG as well as odds of reaching target HbA1c <7%. For weight, canagliflozin 300 mg was superior to liraglutide 1.2 mg, and SGLT-2s were generally associated with larger change from baseline in weight. For risk of major or minor hypoglycemia, no differences were found between treatments.

Conclusions: Compared to SGLT-2 inhibitors, liraglutide offers improvement in HbA1c and FPG. Reductions in weight are likely comparable between liraglutide and SGLT-2s. Liraglutide did not differ from SGLT-2s in terms of risk of hypoglycemia. Given the lack of head-to-head evidence, this analysis provides valuable insight into the comparative outcomes of liraglutide versus SGLT-2 inhibitors.

Keywords: Network meta-analysis; Liraglutide; SGLT-2; Comparative efficacy; HbA1c; Weight; Fasting plasma glucose

INTRODUCTION

The worldwide burden of diabetes is increasing, with a projected prevalence of 366 million by 2030 [1]. A number of management strategies are currently in use for type 2 diabetes mellitus (T2DM), a progressive metabolic disorder characterized by a reduction in insulin production and secretion as well as increased insulin resistance. Typically, initial treatment for people with T2DM involves lifestyle changes. Subsequent stages typically involve treatment with oral antidiabetic drugs (OADs), such as metformin or sulfonylureas (SUs), or GLP-1 receptor agonists (RAs). Clinical guidelines published by the American Association of Clinical Endocrinologists and American College of Endocrinology in 2016

recommend lifestyle therapy plus GLP-1 receptor agonist monotherapy as an acceptable alternative to initial therapy with metformin for select patients with recent-onset T2DM or with mild hyperglycemia (HbA1c <7.5%) [2]. However, the 2016 American Diabetes Association guidelines maintain that metformin is the preferred initial treatment option, unless contraindicated. The addition of a second oral agent, a GLP-1 receptor agonist, or basal insulin is recommended for patients where management with maximum-dose non-insulin monotherapy is inadequate after 3 months of treatment [3].

Liraglutide is a once-daily GLP-1 RA that has been evaluated and shown to be effective and safe in randomized controlled trials (RCTs) and real-world studies throughout the T2DM treatment spectrum. Previous reviews have highlighted the improved glycemic control and favorable safety profile of the GLP-1 RA class of drugs [4–8].

Sodium-glucose cotransporter 2 inhibitors (SGLT-2 inhibitors) are a novel class of once-daily OADs that target the kidneys, increasing urinary glucose excretion. As these treatments act independently of insulin, they have been found to be effective throughout the T2DM spectrum [9–11]. Evidence from several reviews of the clinical literature suggests that SGLT-2 inhibitors improve glycemic control while also offering a favorable weight profile and a low risk of hypoglycemia [9, 11–14].

Liraglutide and SGLT-2 inhibitors have not been compared against each other in head-to-head trials. Through a network meta-analysis (NMA) framework, which permits estimation of the relative treatment effects of interventions that have not been compared against each other in an RCT, we assessed the relative efficacy of liraglutide against SGLT-2 inhibitors among people with

T2DM with inadequate glycemic control despite treatment with metformin alone or in combination with other OADs.

METHODS

Study Identification

A systematic literature review encompassing intervention search terms for liraglutide, canagliflozin, dapagliflozin, and empagliflozin for T2DM was conducted from inception to October 2014. For the purposes of the current analysis, the literature search was updated with terms specific to liraglutide and SGLT-2 inhibitors to identify recent relevant publications. In all iterations of the literature review, MEDLINE, Embase, and the Cochrane Register of Controlled Trials (CENTRAL) were searched to identify relevant RCTs of adults (≥ 18 years) with T2DM who have inadequate HbA1c control despite a stable regimen of metformin (alone or in combination with SU, TZD, or DPP-4). RCTs assessing liraglutide 1.2 mg, liraglutide 1.8 mg, canagliflozin 100 mg, canagliflozin 300 mg, dapagliflozin 5 mg, dapagliflozin 10 mg, empagliflozin 10 mg, or empagliflozin 25 mg were eligible for inclusion in the current analysis. Eligible active comparators were any agent from the TZD or DPP-4 class as well as basal insulin. The full PICOS (Population, Interventions, Comparisons, Outcomes, Study) design statement is described in Supporting Information 1. The search strategies are presented in Supporting Information 2.

Data Extraction and Outcomes

Two reviewers, independently and in duplicate, extracted data on study and patient characteristics, treatment details, and outcomes of interest from each included

publication. The following baseline patient characteristics were extracted: age (years); sex (% female); race/ethnicity (% white, % black, % Asian, % Hispanic); weight (kg); BMI (kg/m^2); HbA1c (%); and duration of diabetes (years). For the continuous outcomes of interest (HbA1c, weight, fasting plasma glucose (FPG)) the change from baseline (CFB) was extracted whenever available, along with corresponding sample size, and measures of uncertainty for all relevant intervention groups. For publications where CFB was not reported, the CFB was calculated as the difference in value at baseline and end of treatment.

Statistical Analyses

For each outcome of interest, we performed a Bayesian NMA to compare the efficacy and safety of liraglutide to those of SGLT-2 inhibitors. NMA methodology allows for the combination of direct and indirect evidence [15] and this approach is widely accepted by decision-makers in the context of health technology assessment [16]. For the continuous outcomes, change from baseline (CFB) in HbA1c, FPG, and weight, a regression model with a normal likelihood distribution and identity link was used, while a binomial likelihood distribution and logit link were used for the proportion of patients meeting HbA1c target as well as the proportion of patients experiencing hypoglycemia.

In order to evaluate the consistency between direct and indirect comparisons, edge-splitting was performed [17]. This iterative technique involves splitting the available evidence into direct and indirect information for each comparison for which both are available. For each treatment comparison in the network, two relative treatment effects are estimated: one with pairwise comparison models based on

direct comparisons and one based on an NMA of the remaining studies using indirect evidence only. After this assessment of inconsistency, the Bucher test was performed for each three-sided loop [18]. Both fixed-effects and random-effects models were fitted to the data using Bayesian Markov Chain Monte Carlo (MCMC) methods, and these models were compared using the deviance information criterion (DIC) to determine whether the random- or fixed-effects model was more appropriate [19].

For analyses of continuous outcomes, we present mean differences (MDs) and 95% credible intervals (CrIs) from the posterior distribution of relative treatment effects. For the proportion of patients meeting HbA1c target values, results are presented as odds ratios (ORs) with corresponding 95% CrIs. In line with Bayesian statistics, statistical superiority (akin to statistical significance with frequentist statistics) was asserted when the 95% credible intervals precluded the null effect (i.e., 0.0 for MDs and 1.0 for ORs). All analyses were performed using R version 3.0.3 and OpenBUGS version 3.2.3 (OpenBUGS Project Management Group).

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Study Identification and Selection

A total of 21,554 abstracts were identified through the systematic literature search. From the 604 full-text publications included in the broader scope review, 28 publications describing 16 RCTs were selected for inclusion [20–35]. Throughout this process, the identification of eligible trials followed the PICOS design criteria outlined in Supporting Information 1. The database search for relevant studies is outlined in Supporting Information 2. The flow of information diagram is presented in Fig. 1.

The complete network of evidence is shown in Fig. 2 and networks are presented by clinical outcome in Supporting Information 3. In

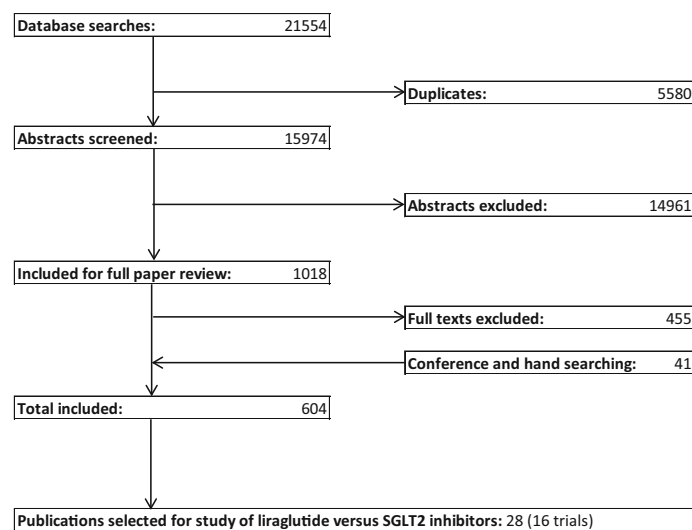


Fig. 1 Flow of information

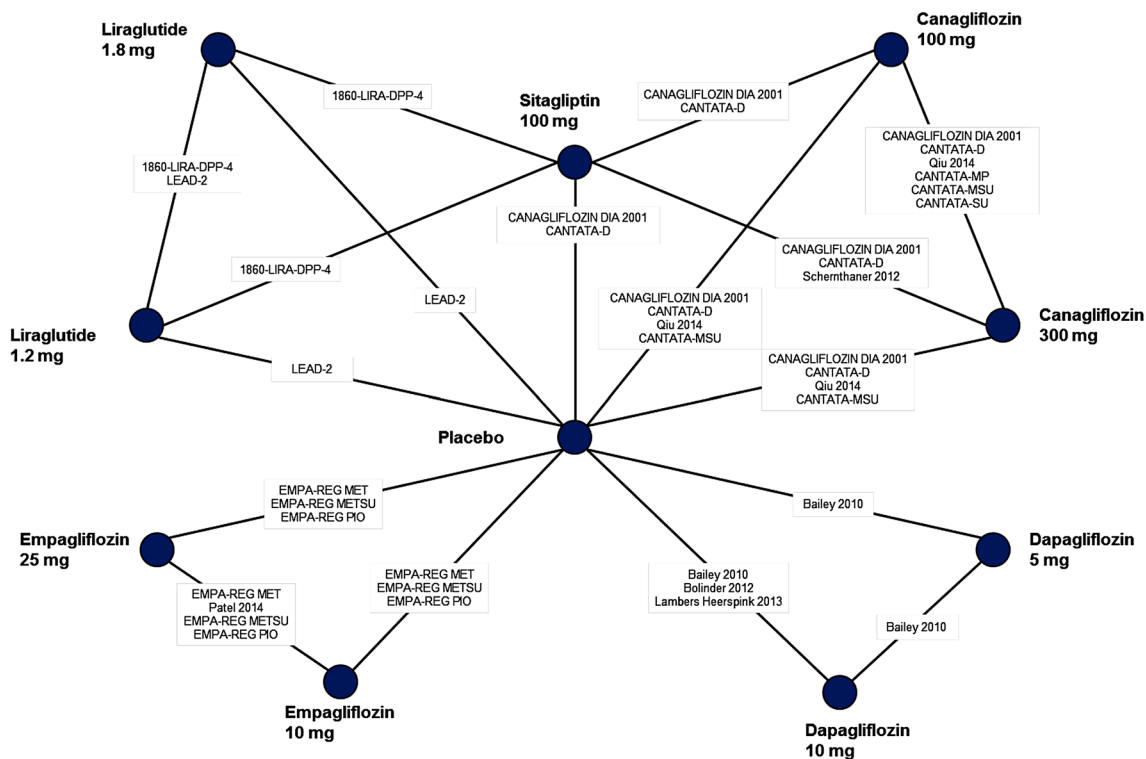


Fig. 2 Overall network of evidence

summary, two studies assessed liraglutide [20, 32], four studies assessed empagliflozin [28–30, 33], seven studies assessed canagliflozin [23–27, 34, 35], three studies assessed dapagliflozin [21, 22, 31], and four studies assessed sitagliptin [20, 23, 24, 35]. Sitagliptin was included in the network to provide indirect evidence to the comparison of liraglutide with SGLT-2 inhibitors.

Studies were generally well matched in terms of baseline age, percentage of female patients, weight, and baseline HbA1c (Table 1). For HbA1c, however, the average trial baseline values in the SGLT-2 trials spanned from 7.2% to 8.1%, whereas the average trial baseline value was 8.4% in both liraglutide trials. Mean duration of diabetes varied from 4 to 9.7 years. Most studies incorporated treatment durations of approximately 26 weeks, though there was some deviation, with two studies having treatment durations of 12 weeks [23, 31] or

52 weeks [27, 35]. With respect to inclusion of 12-week studies, the NMA focuses on comparative effects between interventions, rather than absolute reductions. Thus, while stability of the treatment is generally expected to be reached between 12 and 24 weeks, little to no confounding by differences in time points is expected on comparative effects. Further, additional evidence comes with the advantage of strengthening the evidence base. Change from baseline for each outcome, as reported in each RCT, is presented in Supporting Information 4.

Network Meta-Analyses

A random-effects NMA model was used to estimate outcomes for change in HbA1c, proportion of patients achieving HbA1c targets, mean change in FPG, and mean change in weight as the DIC suggested a better

Table 1 Characteristics of included RCTs

Randomized controlled trial	Treatment duration (weeks)	Concomitant treatment	Intervention	Number of people	Age, years	n (%) female	n (%) white	Disease duration, years	Weight, kg	HbA1c, %
1860-LIRA-DPP-4 [20]	26	Metformin	Liraglutide 1.2 mg	225	56 (10)	109 (48)	184 (82)	6.0 (4.5)	94 (18)	8.4 (0.8)
			Liraglutide 1.8 mg	221	55 (9)	105 (48)	193 (87)	6.4 (5.4)	95 (18)	8.4 (0.7)
			Sitagliptin 100 mg	219	55 (9)	99 (45)	199 (91)	6.3 (5.4)	93 (19)	8.5 (0.7)
Bailey et al. [21]	24	Metformin	Placebo	137	54 (10)	58 (45)		5.8 (5.1)	88 (19)	8.1 (1.0)
			Dapagliflozin 5 mg	137	54 (9)	64 (50)		6.4 (5.8)	85 (16)	8.2 (1.0)
			Dapagliflozin 10 mg	135	53 (10)	55 (43)		6.1 (5.4)	86 (18)	7.9 (0.8)
Bolinder et al. [22]	24	Metformin	Placebo	91	61 (7)	40 (44)	91 (100)	5.5 (5.3)	91 (14)	7.2 (0.5)
			Dapagliflozin 10 mg	91	61 (8)	40 (45)	89 (100)	6.0 (4.5)	92 (14)	7.2 (0.4)
CANAGLIFLOZIN DIA 2001 [23]	12	Metformin	Placebo	65	53 (8)	34 (52)		6.4 (5.0)	86 (20)	7.8 (0.8)
			Canagliflozin 100 mg	64	52 (8)	28 (44)		6.1 (4.7)	88 (16)	7.8 (1.0)
			Canagliflozin 300 mg	64	52 (7)	28 (44)		5.9 (5.2)	87 (16)	7.7 (1.0)
			Sitagliptin 100 mg	65	52 (8)	27 (42)		5.6 (4.7)	87 (18)	7.6 (1.0)

Table 1 continued

Randomized controlled trial	Treatment duration (weeks)	Concomitant treatment	Intervention	Number of people	Age, years	n (%) female	n (%) white	Disease duration, years	Weight, kg	HbA1c, %
CANTATA-D [24]	26	Metformin	Placebo	183	55 (10)	89 (49)	129 (71)	6.8 (5.3)	87 (22)	8.0 (0.9)
			Sitagliptin 100 mg	366	56 (10)	194 (53)	264 (72)	6.8 (5.2)	88 (22)	7.9 (0.9)
			Canagliflozin 100 mg	368	56 (9)	194 (53)	252 (69)	6.7 (5.4)	89 (22)	7.9 (0.9)
CANTATA-MP [25]	26	Metformin + pioglitazone	Canagliflozin 100 mg	114	55 (9)	202 (55)	256 (70)	7.1 (5.4)	85 (21)	7.9 (0.9)
			Canagliflozin 300 mg	367						
			Canagliflozin 100 mg	114						
CANTATA-MSU [26]	26	Metformin + sulfonyleurea	Placebo	156	57 (8)	80 (51)	128 (82)	10.3 (6.7)	91 (23)	8.1 (0.9)
			Canagliflozin 100 mg	157	57 (11)	81 (52)	132 (84)	9.0 (5.7)	94 (23)	8.1 (0.9)
			Canagliflozin 300 mg	156	56 (9)	69 (44)	127 (81)	9.4 (6.4)	94 (22)	8.1 (0.9)
CANTATA-SU [27]	52	Metformin	Canagliflozin 100 mg	483	56 (10)	231 (48)	323 (67)	6.5 (5.5)	87 (20)	7.8 (0.8)
			Canagliflozin 300 mg	485	56 (9)	244 (50)	333 (69)	6.7 (5.5)	87 (20)	7.8 (0.8)
			Placebo	207	56 (10)	91 (44)	113 (55)		80 (19)	7.9 (0.9)
EMPA-REG MET [28]	24	Metformin	Empagliflozin 25 mg	213	56 (10)	93 (44)	113 (53)		82 (19)	7.9 (0.9)
			Empagliflozin 10 mg	217	56 (10)	92 (42)	112 (52)		82 (19)	7.9 (0.8)

Table 1 continued

Randomized controlled trial	Treatment duration (weeks)	Concomitant treatment	Intervention	Number of people	Age, years	n (%) female	n (%) white	Disease duration, years	Weight, kg	HbA1c, %
EMPA-REG METSU [29]	24	Metformin + sulfonylurea	Placebo	225	57 (9)	113 (50)	88 (39)		76 (17)	8.2 (0.8)
			Empagliflozin 25 mg	216	57 (9)	102 (47)	85 (39)		78 (19)	8.1 (0.8)
EMPA-REG PIO [30]	24	Metformin + pioglitazone	Placebo	165	55 (11)	92 (56)	60 (36)		78 (20)	8.2 (0.9)
			Empagliflozin 10 mg	165	55 (10)	82 (50)	69 (42)		78 (19)	8.1 (0.9)
Lambers Heerspink et al. [31]	12	Metformin ± sulfonylurea	Empagliflozin 25 mg	168	54 (9)	83 (49)	68 (41)		79 (20)	8.1 (0.8)
			Placebo	25	58 (10)	7 (28)		6.5 (5.0)	96 (20)	7.5 (1.0)
LEAD-2 [32]	29	Metformin	Dapagliflozin 10 mg	24	54 (9)	8 (32)		6.5 (4.4)	93 (18)	7.0 (0.6)
			Placebo	122	56 (9)	48 (40)		8.0 (6.0)		8.4 (1.1)
Patel et al. [33]	24	Metformin	Liraglutide 1.2 mg	241	57 (9)	110 (46)		7.0 (5.0)		8.3 (1.0)
			Liraglutide 1.8 mg	242	57 (9)	99 (41)		8.0 (5.0)		8.4 (1.0)
Patel et al. [33]	24	Metformin	Empagliflozin 25 mg	141	56 (10)				86 (19)	8.1
			Empagliflozin 10 mg	140	56 (10)				86 (19)	8.0

Table 1 continued

Randomized controlled trial	Treatment duration (weeks)	Concomitant treatment	Intervention	Number of people	Age, years	n (%) female	n (%) white	Disease duration, years	Weight, kg	HbA1c, %
Qiu et al. [34]	18	Metformin	Placebo	93						7.6
			Canagliflozin 100 mg	93						7.6
			Canagliflozin 300 mg	93						7.6
Schernthaner et al. [35]	52	Metformin	Canagliflozin 300 mg	377	57 (10)	170 (45)	245 (65)	9.4 (6.1)	87 (23)	8.1 (0.9)
			Sitagliptin 100 mg	378	57 (9)	163 (43)	240 (64)	9.7 (6.3)	89 (23)	8.1 (0.9)

All estimates presented as mean (standard deviation)

model fit. A fixed-effects NMA was found to be more appropriate for estimating major and mild hypoglycemia outcomes, as results could not reach MCMC convergence under the random-effects model. The results of the edge-splitting exercise, which was used to compare outcomes as determined by indirect and direct evidence separately, are presented in Supporting Information 5.

HbA1c

Table 2 presents mean differences in CFB in HbA1c (%). All interventions were statistically superior to placebo, with liraglutide 1.2 and 1.8 mg offering the largest reductions compared to placebo (MD -1.02%, 95% CrI -1.28 to -0.73, and MD -1.18%, 95% CrI -1.45 to -0.89, respectively). Both doses of liraglutide were also statistically superior to all other doses of SGLT-2s, with the exception of the comparison between liraglutide 1.2 mg and canagliflozin 300 mg. Both doses of liraglutide were also found to be statistically superior to sitagliptin 100 mg in terms of HbA1c reduction.

The expected changes in HbA1c for each active intervention were modeled by combining the average placebo response with the relative treatment effect estimates of each treatment versus placebo (Fig. 3). However, as each modeled response also includes uncertainty in the average placebo response, this figure should not be used to make statistical comparisons between treatments.

HbA1c Target

The odds ratios of achieving target HbA1c levels (<7% or ≤7%, depending on the target defined in the respective RCT) are presented in Table 3. All treatments, with the exception of dapagliflozin 5 mg, were found to be statistically more efficacious than placebo in achieving HbA1c targets. Liraglutide 1.8 mg

Table 2 Change from baseline in HbA1c between treatments (%)

Placebo	1.02 (0.73, 1.28)	1.18 (0.89, 1.45)	0.64 (0.51, 0.76)	0.79 (0.67, 0.91)	0.37 (0.23, 0.53)	0.31 (0.09, 0.55)	0.59 (0.47, 0.72)	0.61 (0.49, 0.74)	0.58 (0.44, 0.73)
-1.02 (-1.28, -0.73)	Liraglutide 1.2 mg	0.17 (-0.02, 0.35)	-0.37 (-0.67, -0.08)	-0.23 (-0.51, 0.07)	-0.64 (-0.94, -0.32)	-0.70 (-1.05, -0.33)	-0.42 (-0.72, -0.11)	-0.41 (-0.71, -0.09)	-0.43 (-0.73, -0.12)
-1.18 (-1.45, -0.89)	-0.17 (-0.35, 0.02)	Liraglutide 1.8 mg	-0.54 (-0.84, -0.24)	-0.39 (-0.69, -0.09)	-0.81 (-1.11, -0.48)	-0.87 (-1.22, -0.49)	-0.59 (-0.88, -0.27)	-0.57 (-0.87, -0.25)	-0.60 (-0.90, -0.28)
-0.64 (-0.76, -0.51)	0.37 (0.08, 0.67)	0.54 (0.24, 0.84)	Canagliflozin 100 mg	0.15 (0.06, 0.24)	-0.27 (-0.45, -0.07)	-0.32 (-0.58, -0.06)	-0.04 (-0.22, 0.13)	-0.03 (-0.20, 0.15)	-0.05 (-0.18, 0.07)
-0.79 (-0.91, -0.67)	0.23 (-0.07, 0.51)	0.39 (0.09, 0.69)	-0.15 (-0.24, -0.06)	Canagliflozin 300 mg	-0.42 (-0.60, -0.22)	-0.47 (-0.72, -0.21)	-0.19 (-0.37, -0.02)	-0.18 (-0.35, -0.00)	-0.20 (-0.33, -0.09)
-0.37 (-0.53, -0.23)	0.64 (0.32, 0.94)	0.81 (0.48, 1.11)	0.27 (0.07, 0.45)	0.42 (0.22, 0.60)	Dapagliflozin 10 mg	-0.06 (-0.28, 0.17)	0.22 (0.02, 0.41)	0.24 (0.04, 0.42)	0.21 (-0.00, 0.41)
-0.31 (-0.55, -0.09)	0.70 (0.33, 1.05)	0.87 (0.49, 1.22)	0.32 (0.06, 0.58)	0.47 (0.21, 0.72)	0.06 (-0.17, 0.28)	Dapagliflozin 5 mg	0.28 (0.02, 0.54)	0.30 (0.04, 0.55)	0.27 (-0.01, 0.53)
-0.59 (-0.72, -0.47)	0.42 (0.11, 0.72)	0.59 (0.27, 0.88)	0.04 (-0.13, 0.22)	0.19 (0.02, 0.37)	-0.22 (-0.41, -0.02)	-0.28 (-0.54, -0.02)	Empagliflozin 10 mg	0.02 (-0.10, 0.13)	-0.01 (-0.21, 0.18)
-0.61 (-0.74, -0.49)	0.41 (0.09, 0.71)	0.57 (0.25, 0.87)	0.03 (-0.15, 0.20)	0.18 (0.00, 0.35)	-0.24 (-0.42, -0.04)	-0.30 (-0.55, -0.04)	-0.02 (-0.13, 0.10)	Empagliflozin 25 mg	-0.03 (-0.22, 0.16)
-0.58 (-0.73, -0.44)	0.43 (0.12, 0.73)	0.60 (0.28, 0.90)	0.05 (-0.07, 0.18)	0.20 (0.09, 0.33)	-0.21 (-0.41, 0.00)	-0.27 (-0.53, 0.01)	0.01 (-0.18, 0.21)	0.03 (-0.16, 0.22)	Sitagliptin 100 mg

Each cell represents the comparison (mean difference and 95% CrI) of the row treatment versus the column treatment. All values in bold are statistically significant at the 0.05 significance level. DIC 72.36, deviance 41.53, SD 0.06

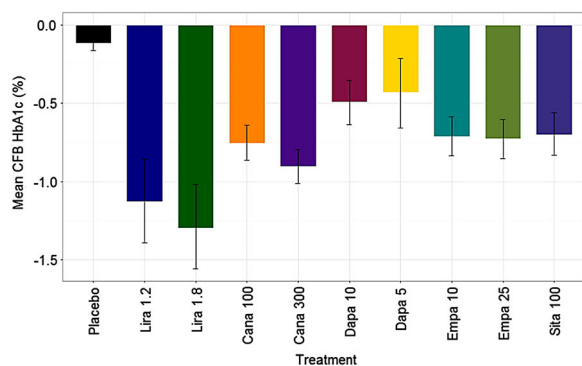


Fig. 3 Modelled outcomes in change from baseline in HbA1c (%) in metformin-experienced T2DM patients. Bars represent the estimated mean response and whiskers represent the 95% CrI. The estimate for placebo is a pooled response estimate based on the available data

provided the highest odds of achieving target HbA1c compared to placebo (OR 9.80, 95% CrI 5.61–16.65) followed by liraglutide 1.2 mg (OR 6.51, 95% CrI 3.67–10.99). Liraglutide 1.8 mg was statistically superior to any other treatment. Similar trends were observed for liraglutide 1.2 mg, although no statistical superiority could be asserted for the comparisons to both empagliflozin doses.

FPG

Table 4 presents mean differences in CFB in FPG (mmol/dL) for each comparison in the network. All interventions in the network performed statistically superiorly to placebo in lowering FPG, with the greatest reduction seen with liraglutide 1.8 mg (MD -2.20 mmol/dL, 95% CrI -2.63 to -1.77). Liraglutide statistically lowered FPG compared to both doses of dapagliflozin. No statistical differences were observed when comparing high to high and low to low doses of liraglutide, canagliflozin, and empagliflozin.

Weight

Mean differences in CFB in weight are presented in Table 5. Liraglutide and all SGLT-2 inhibitors were associated with weight reductions that were statistically superior to placebo. Liraglutide generally appeared statistically comparable to all SGLT-2 inhibitors, and statistically superior to sitagliptin, albeit canagliflozin 300 mg was statistically superior to liraglutide 1.2 mg.

Table 3 Odds ratio for proportion of patients achieving HbA1c targets (<7% or ≤7%)

Placebo	0.15 (0.09, 0.27)	0.10 (0.06, 0.18)	0.44 (0.30, 0.65)	0.28 (0.19, 0.41)	0.42 (0.21, 0.79)	0.60 (0.30, 1.17)	0.26 (0.16, 0.40)	0.22 (0.14, 0.35)	0.40 (0.27, 0.60)
6.51 (3.67, 10.99)	Liraglutide 1.2 mg	0.66 (0.45, 0.97)	2.90 (1.56, 4.95)	1.84 (1.00, 3.07)	2.70 (1.11, 6.11)	3.90 (1.59, 9.01)	1.67 (0.80, 3.35)	1.43 (0.67, 2.84)	2.60 (1.56, 4.18)
9.80 (5.61, 16.65)	1.51 (1.03, 2.23)	Liraglutide 1.8 mg	4.38 (2.38, 7.49)	2.77 (1.55, 4.63)	4.07 (1.68, 9.26)	5.91 (2.39, 13.52)	2.51 (1.21, 5.14)	2.15 (1.03, 4.32)	3.91 (2.39, 6.30)
2.25 (1.54, 3.32)	0.34 (0.20, 0.64)	0.23 (0.13, 0.42)	Canagliflozin 100 mg	0.63 (0.47, 0.85)	0.93 (0.43, 1.99)	1.35 (0.62, 2.90)	0.58 (0.32, 1.06)	0.49 (0.27, 0.90)	0.90 (0.63, 1.34)
3.54 (2.47, 5.17)	0.54 (0.33, 1.00)	0.36 (0.22, 0.65)	1.58 (1.18, 2.13)	Canagliflozin 300 mg	1.47 (0.67, 3.10)	2.13 (0.98, 4.58)	0.91 (0.51, 1.66)	0.78 (0.43, 1.42)	1.41 (1.04, 2.02)
2.40 (1.26, 4.70)	0.37 (0.16, 0.90)	0.25 (0.11, 0.59)	1.07 (0.50, 2.32)	0.68 (0.32, 1.49)	Dapagliflozin 10 mg	1.45 (0.77, 2.74)	0.62 (0.28, 1.39)	0.52 (0.24, 1.18)	0.96 (0.45, 2.15)
1.67 (0.86, 3.29)	0.26 (0.11, 0.63)	0.17 (0.07, 0.42)	0.74 (0.34, 1.62)	0.47 (0.22, 1.02)	0.69 (0.37, 1.30)	Dapagliflozin 5 mg	0.43 (0.19, 0.96)	0.36 (0.16, 0.82)	0.67 (0.31, 1.50)
3.89 (2.47, 6.25)	0.60 (0.30, 1.26)	0.40 (0.19, 0.83)	1.73 (0.95, 3.16)	1.10 (0.60, 1.98)	1.62 (0.72, 3.57)	2.34 (1.04, 5.34)	Empagliflozin 10 mg	0.85 (0.56, 1.27)	1.55 (0.86, 2.93)
4.57 (2.88, 7.29)	0.70 (0.35, 1.48)	0.47 (0.23, 0.97)	2.04 (1.12, 3.73)	1.29 (0.71, 2.33)	1.91 (0.85, 4.20)	2.74 (1.22, 6.26)	1.18 (0.78, 1.78)	Empagliflozin 25 mg	1.83 (1.00, 3.44)
2.50 (1.66, 3.69)	0.38 (0.24, 0.64)	0.26 (0.16, 0.42)	1.12 (0.75, 1.59)	0.71 (0.49, 0.96)	1.04 (0.47, 2.21)	1.50 (0.66, 3.24)	0.64 (0.34, 1.17)	0.55 (0.29, 1.00)	Sitagliptin 100 mg

Estimates generated from random-effects model. Each cell represents the estimated comparative effect (odds ratio and 95% credible interval) of the row treatment versus the column treatment. All values in bold are statistically significant at the 0.05 significance level. DIC 47.15, deviance 25.55, SD 0.17

Table 4 Change from baseline in fasting plasma glucose between treatments (mmol/dL)

Placebo	2.03 (1.59, 2.45)	2.20 (1.77, 2.63)	1.68 (1.36, 1.98)	2.05 (1.74, 2.34)	1.00 (0.63, 1.38)	0.87 (0.37, 1.41)	1.47 (1.00, 1.94)	1.59 (1.13, 2.06)	1.00 (0.67, 1.29)
-2.03 (-2.45, -1.59)	Liraglutide 1.2 mg	0.17 (-0.20, 0.56)	-0.35 (-0.83, 0.13)	0.02 (-0.45, 0.49)	-1.03 (-1.58, -0.44)	-1.16 (-1.81, -0.46)	-0.57 (-1.19, 0.08)	-0.44 (-1.07, 0.20)	-1.03 (-1.46, -0.61)
-2.20 (-2.63, -1.77)	-0.17 (-0.56, 0.20)	Liraglutide 1.8 mg	-0.53 (-1.01, -0.04)	-0.15 (-0.63, 0.34)	-1.21 (-1.75, -0.61)	-1.33 (-1.99, -0.63)	-0.74 (-1.36, -0.09)	-0.61 (-1.24, 0.03)	-1.20 (-1.64, -0.76)
-1.68 (-1.98, -1.36)	0.35 (-0.13, 0.83)	0.53 (0.04, 1.01)	Canagliflozin 100 mg	0.38 (0.11, 0.63)	-0.67 (-1.16, -0.18)	-0.80 (-1.41, -0.17)	-0.21 (-0.76, 0.36)	-0.09 (-0.64, 0.48)	-0.68 (-1.00, -0.36)
-2.05 (-2.34, -1.74)	-0.02 (-0.49, 0.45)	0.15 (-0.34, 0.63)	-0.38 (-0.63, -0.11)	Canagliflozin 300 mg	-1.05 (-1.53, -0.55)	-1.18 (-1.79, -0.56)	-0.59 (-1.13, -0.02)	-0.46 (-1.00, 0.10)	-1.05 (-1.34, -0.77)
-1.00 (-1.38, -0.63)	1.03 (0.44, 1.58)	1.21 (0.61, 1.75)	0.67 (0.18, 1.16)	1.05 (0.55, 1.53)	Dapagliflozin 10 mg	-0.12 (-0.65, 0.39)	0.46 (-0.16, 1.06)	0.59 (-0.02, 1.18)	0.00 (-0.52, 0.48)
-0.87 (-1.41, -0.37)	1.16 (0.46, 1.81)	1.33 (0.63, 1.99)	0.80 (0.17, 1.41)	1.18 (0.56, 1.79)	0.12 (-0.39, 0.65)	Dapagliflozin 5 mg	0.59 (-0.12, 1.28)	0.72 (0.00, 1.41)	0.12 (-0.52, 0.72)
-1.47 (-1.94, -1.00)	0.57 (-0.08, 1.19)	0.74 (0.09, 1.36)	0.21 (-0.36, 0.76)	0.59 (0.02, 1.13)	-0.46 (-1.06, 0.16)	-0.59 (-1.28, 0.12)	Empagliflozin 10 mg	0.13 (-0.34, 0.59)	-0.46 (-1.04, 0.08)
-1.59 (-2.06, -1.13)	0.44 (-0.20, 1.07)	0.61 (-0.03, 1.24)	0.09 (-0.48, 0.64)	0.46 (-0.10, 1.00)	-0.59 (-1.18, 0.02)	-0.72 (-1.41, -0.00)	-0.13 (-0.59, 0.34)	Empagliflozin 25 mg	-0.59 (-1.17, 0.00)
-1.00 (-1.29, -0.67)	1.03 (0.61, 1.46)	1.20 (0.76, 1.64)	0.68 (0.36, 1.00)	1.05 (0.77, 1.34)	-0.00 (-0.48, 0.52)	-0.12 (-0.72, 0.52)	0.46 (-0.08, 1.04)	0.59 (-0.00, 1.17)	Sitagliptin 100 mg

Each cell represents the comparison (mean difference and 95% CrI) of the row treatment versus the column treatment. All values in bold are statistically significant at the 0.05 significance level. DIC 53.92, deviance 29.3, SD 0.16

Hypoglycemic Events

Both major and minor hypoglycemic events were considered separately in the NMA and no differences were observed between the treatments for which data were available. For

major hypoglycemic events, data were available for liraglutide, canagliflozin, dapagliflozin, empagliflozin, and sitagliptin. The available data for minor hypoglycemic events was more limited, with outcomes only available for

Table 5 Change from baseline in weight (kg) between treatments

Placebo	1.27 (0.61, 1.90)	1.59 (0.96, 2.24)	1.73 (1.25, 2.20)	2.27 (1.79, 2.71)	2.05 (1.44, 2.66)	2.12 (1.39, 2.86)	1.70 (1.26, 2.13)	2.00 (1.56, 2.44)	-0.49 (-0.96, 0.01)
-1.27 (-1.90, -0.61)	Liraglutide 1.2 mg	0.32 (-0.23, 0.86)	0.46 (-0.27, 1.19)	0.99 (0.31, 1.71)	0.79 (-0.11, 1.66)	0.86 (-0.14, 1.82)	0.44 (-0.36, 1.23)	0.74 (-0.05, 1.53)	-1.75 (-2.39, -1.09)
-1.59 (-2.24, -0.96)	-0.32 (-0.86, 0.23)	Liraglutide 1.8 mg	0.15 (-0.59, 0.83)	0.68 (-0.03, 1.35)	0.47 (-0.44, 1.35)	0.54 (-0.46, 1.50)	0.12 (-0.68, 0.88)	0.42 (-0.38, 1.19)	-2.07 (-2.73, -1.43)
-1.73 (-2.20, -1.25)	-0.46 (-1.19, 0.27)	-0.15 (-0.83, 0.59)	Canagliflozin 100 mg	0.53 (0.14, 0.94)	0.32 (-0.43, 1.11)	0.38 (-0.47, 1.27)	-0.03 (-0.67, 0.62)	0.27 (-0.37, 0.93)	-2.22 (-2.67, -1.73)
-2.27 (-2.71, -1.79)	-0.99 (-1.71, -0.31)	-0.68 (-1.35, 0.03)	-0.53 (-0.94, -0.14)	Canagliflozin 300 mg	-0.20 (-0.98, 0.55)	-0.14 (-1.02, 0.73)	-0.56 (-1.20, 0.07)	-0.26 (-0.89, 0.38)	-2.74 (-3.16, -2.32)
-2.05 (-2.66, -1.44)	-0.79 (-1.66, 0.11)	-0.47 (-1.35, 0.44)	-0.32 (-1.11, 0.43)	0.20 (-0.55, 0.98)	Dapagliflozin 10 mg	0.06 (-0.66, 0.80)	-0.35 (-1.11, 0.41)	-0.05 (-0.81, 0.69)	-2.54 (-3.31, -1.75)
-2.12 (-2.86, -1.39)	-0.86 (-1.82, 0.14)	-0.54 (-1.50, 0.46)	-0.38 (-1.27, 0.47)	0.14 (-0.73, 1.02)	-0.06 (-0.80, 0.66)	Dapagliflozin 5 mg	-0.42 (-1.29, 0.44)	-0.12 (-0.98, 0.72)	-2.61 (-3.48, -1.71)
-1.70 (-2.13, -1.26)	-0.44 (-1.23, 0.36)	-0.12 (-0.88, 0.68)	0.03 (-0.62, 0.67)	0.56 (-0.07, 1.20)	0.35 (-0.41, 1.11)	0.42 (-0.44, 1.29)	Empagliflozin 10 mg	0.30 (-0.14, 0.75)	-2.19 (-2.83, -1.51)
-2.00 (-2.44, -1.56)	-0.74 (-1.53, 0.05)	-0.42 (-1.19, 0.38)	-0.27 (-0.93, 0.37)	0.26 (-0.38, 0.89)	0.05 (-0.69, 0.81)	0.12 (-0.72, 0.98)	-0.30 (-0.75, 0.14)	Empagliflozin 25 mg	-2.49 (-3.14, -1.81)
0.49 (-0.01, 0.96)	1.75 (1.09, 2.39)	2.07 (1.43, 2.73)	2.22 (1.73, 2.67)	2.74 (2.32, 3.16)	2.54 (1.75, 3.31)	2.61 (1.71, 3.48)	2.19 (1.51, 2.83)	2.49 (1.81, 3.14)	Sitagliptin 100 mg

Each cell represents the comparison (mean difference and 95% CrI) of the row treatment versus the column treatment. All values in bold are statistically significant at the 0.05 significance level. DIC 55.76, deviance 31.85, SD 0.18

liraglutide and dapagliflozin. The results of these analyses are summarized in Supporting Information 6; no statistically meaningful differences were found between any of the considered interventions.

DISCUSSION

The purpose of this NMA was to compare the efficacy of liraglutide to SGLT-2 inhibitors among people with inadequately controlled T2DM despite treatment with metformin (alone or in combination with other OADs). Across all outcomes evaluated in this analysis, liraglutide performed at least as well as SGLT-2 inhibitors. Management with liraglutide was found to present larger reductions in CFB in HbA1c or FPG, and reaching HbA1c targets (<7% or ≤7%). Differences between treatments based on these outcomes were particularly marked for comparisons to liraglutide 1.8 mg. Moreover, liraglutide 1.8 mg was generally associated with more favorable outcomes. Few

differences between liraglutide and SGLT-2 inhibitors in CFB in weight were observed. This finding suggests that there are no weight-related consequences associated with the use of liraglutide over the use of other T2DM treatments included in our analysis. Overall, the analyses indicated better efficacy outcomes with liraglutide.

No differences were observed in terms of hypoglycemia. However, this outcome must be interpreted with caution, given the low numbers of hypoglycemic events observed in the included trials and, in the case of minor hypoglycemia, the limited number of interventions that were available for inclusion in the network.

The population included people previously treated with metformin monotherapy as well as those on metformin in combination with other OADs, including SUs, TZDs, and DPP-4s. The nature of the evidence base did not allow for separate NMAs for these subpopulations. As it is possible that the number of prior OADs is an

effect modifier, we cannot ignore the potential of this factor to impart bias or inconsistency into the model. To this end, some differences were observed across trials for baseline disease duration and HbA1c. For the latter, the two included liraglutide studies have slightly higher baseline HbA1c values compared to the SGLT-2 trials. Future studies may also evaluate the effects of differences in baseline HbA1c as well as the duration of treatment. While we did not observe strong evidence of inconsistency between direct and indirect comparisons of relative treatment effects in this population, future analyses may re-evaluate the evidence base to assess the impact of these factors.

In conclusion, liraglutide appears to offer better glycemic control in terms of lowering HbA1c levels, FPG, and achieving HbA1c targets in comparison to SGLT-2 inhibitors. Further, no weight-related consequences associated with the use of liraglutide over the use of SGLT-2s were observed. No differences were observed between treatments for hypoglycemia events, though this outcome must be interpreted with caution given the limitations of the available data. Overall, liraglutide has been demonstrated as an efficacious treatment option compared to SGLT-2 inhibitors in the management of people with T2DM on background OADs.

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criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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Compliance with ethics guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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