

# Network meta-analysis of lorcaserin and oral hypoglycaemics for patients with type 2 diabetes mellitus and obesity

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## What is already known about this subject

- Initial treatment of type 2 diabetes mellitus (T2DM) includes lifestyle interventions and metformin monotherapy.
- Lorcaserin is 1 of 5 FDA-approved agents for weight loss.
- Lorcaserin is indicated in adults with a body mass index (BMI) of  $\geq 30$  or  $27 \text{ kg m}^{-2}$  and at least one weight-related comorbidity, such as T2DM.

## What this study adds

- Support for lorcaserin as an alternative to second-line glucose lowering therapies in patients with a BMI  $\geq 27 \text{ kg m}^{-2}$ .
- Although not an FDA-approved glucose lowering medication, lorcaserin may be non-inferior to current glucose lowering agents as add-on therapy.
- A network meta-analysis comparing lorcaserin therapy to second-line glucose lowering adjuvant therapy in T2DM.

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## Summary

In addition to weight loss, randomized controlled trials have shown improvement in glycaemic control in patients taking lorcaserin. The aim of this study was to compare adding lorcaserin or other glucose lowering medications to metformin on weight and glycaemic control. A systematic review and network meta-analysis of randomized controlled trials were conducted. Included studies (published 1990–2014) were of lorcaserin or glucose lowering medications in type 2 diabetic patients compared to placebo or different active treatments. Studies had to report  $\geq 1$  key outcome (change in weight or HbA1c, % HbA1c  $< 7$ , hypoglycaemia). Direct meta-analysis was performed using DerSimonian and Laird random effects models, and network meta-analysis with Bayesian Markov-chain Monte Carlo random effects models; 6552 articles were screened and 41 included. Lorcaserin reduced weight significantly more than thiazolidinediones, glinides, sulphonylureas and dipeptidyl peptidase-4 inhibitors, some of which may have led to weight gain. There were no significant differences in weight change between lorcaserin and alpha-glucosidase inhibitors, glucagon-like peptide-1 agonists and sodium/glucose cotransporter 2 inhibitors. Network meta-analysis showed lorcaserin was non-inferior to all other agents on HbA1c reduction and % achieving HbA1c of  $< 7\%$ . The risk of hypoglycaemia was not significantly different among studied agents except that sulphonylureas were associated with higher risk of hypoglycaemia than lorcaserin. Although additional studies are needed, this analysis suggests in a population of patients with a body mass index of  $\geq 27$  who do not achieve glycaemic control on a single agent, lorcaserin may be added as an alternative to an add-on glucose lowering medication.

**Keywords:** Anti-diabetic drug, network meta-analysis, obesity, systematic review, type 2 diabetes.

## Introduction

Type 2 diabetes mellitus (T2DM) affects more than 29 million Americans (1). More than 60% of U.S. patients with diabetes

also have obesity (body mass index or BMI  $\geq 30 \text{ kg m}^{-2}$ ) (2). Initial treatment of T2DM most commonly includes lifestyle interventions to decrease caloric intake and increase physical

activity and metformin monotherapy to reduce blood glucose (3).

Regardless of initial response to metformin monotherapy, the natural progression of T2DM is a gradual rise in blood glucose concentration (4,5). Weight loss improves insulin sensitivity and beta cell function; 42% of patients who experienced HbA1c <7% with first-line metformin monotherapy had disease progression within the 2- to 5-year follow-up period (6). When lifestyle changes and metformin fail to produce glycaemic control in T2DM, the American Association of Clinical Endocrinologists (AACE) guidelines recommend additional glucose lowering medications (7). Dual therapy for T2DM often includes glucagon-like peptide-1 (GLP-1) receptor agonist, sodium/glucose cotransporter 2 (SGLT2) inhibitor and dipeptidyl peptidase-4 (DPP4) antagonist. These second-line medications all reduce glycated haemoglobin (HbA1c), although effects on glycaemic control vary. Some, such as sulphonylureas (SU), are associated with weight gain, which may contribute to insulin resistance and hinder glycaemic control (5,8).

The Food and Drug Administration (FDA) approved lorcaserin, a serotonin-2C agonist, in 2012 as an adjunct to reduced-calorie diet and exercise for chronic weight management. It is indicated in adults with BMI  $\geq 30$  or 27 kg m<sup>-2</sup> and at least one weight-related comorbidity, such as T2DM (9). Lorcaserin suppresses appetite, producing weight loss of more than 5% of baseline body weight after a minimum of one year in significantly more patients compared to placebo (10,11). In a clinical trial evaluating weight loss in patients with T2DM, lorcaserin reduced both HbA1c and fasting plasma glucose significantly more than placebo (12). The American Diabetes Association (ADA) Standards of Medical Care lists lorcaserin as 1 of 5 FDA-approved weight loss agents (8).

We sought to compare the clinical effectiveness of lorcaserin in T2DM with glucose lowering therapies. The number of available glucose lowering agents renders individual pairwise comparisons unrealistic. Furthermore, traditional 2-intervention meta-analyses would not allow for a comparison of all available evidence (13). Therefore, we conducted a systematic review and network meta-analysis of available randomized trials to compare lorcaserin adjuvant therapy to second-line glucose lowering adjuvant therapy in the management of T2DM.

## Methods

### Article identification

A detailed, pre-specified protocol was used. The meta-analysis included randomized controlled trials (RCT) including individuals  $\geq 18$  years with T2DM that studied at least one drug class of interest: alpha-glucoside inhibitors (AGI)

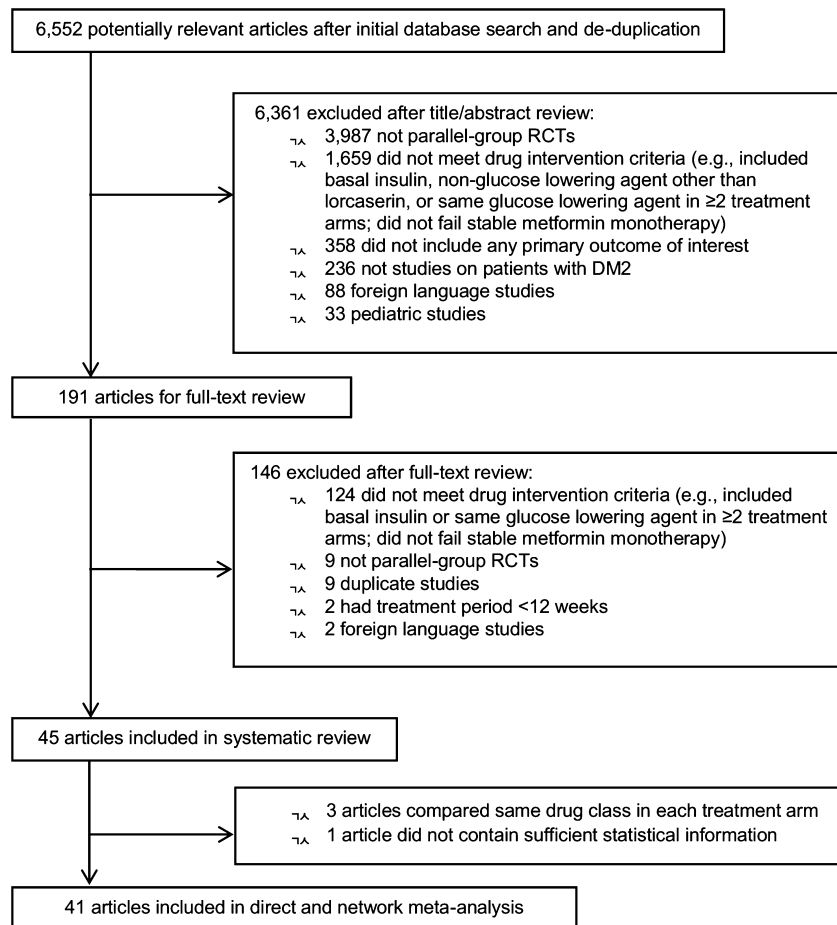
(i.e. acarbose), SUs (i.e. glyburide, glimepiride, tolbutamide, chlorpropamide, gliclazide or glipizide), thiazolidinediones or glitazones (TZD) (i.e. rosiglitazone, pioglitazone or troglitazone), GLP-1 agonists (i.e. exenatide or liraglutide), dipeptidyl peptidase-4 (DPP-4) inhibitors (i.e. vildagliptin, sitagliptin, linagliptin, alogliptin or saxagliptin), meglitinides (i.e. repaglinide or nateglinide), sodium/glucose cotransporter 2 (SGLT-2) inhibitors (i.e. canagliflozin, empagliflozin or dapagliflozin), lorcaserin or placebo; trials not specifying drugs were excluded. Included studies must have subjects treated for minimum of 12 weeks after randomization, compared two different agents (or medication vs. placebo), and reported at least one of the primary study outcomes, selected for their clinical significance: mean change in HbA1c, achievement of HbA1c <7%, mean change in baseline body weight or number of episodes of hypoglycaemia. For treatments other than lorcaserin, both inadequate response to stable metformin monotherapy and use of metformin only as background therapy at randomization were required. During this study, there was only one RCT studying lorcaserin's efficacy in diabetics (12), which we included despite its inclusion of patients who had not failed metformin or were on SU plus metformin, and its comparison of two arms of the same agent. For all agents, RCTs comparing different doses of the same therapeutic agent or studying patients taking basal insulin were excluded. Also excluded: non-English language publications, pediatric-only trials, and non-randomized trials.

### Systematic review

A validated strategy (14), using Medical Subject Headings and keywords, was used to search PubMed, EMBASE, Web of Science and Cochrane CENTRAL for articles of interest published between January 1, 1990 and December 16, 2014. ADA and AACE conference abstracts and proceedings from 2012 to 2014 were reviewed. Searches were supplemented with manual review. Two trained reviewers screened titles and abstracts. Articles accepted after full text review had data abstraction by two reviewers. Disagreements were resolved through discussion. Data abstraction included primary qualifying study outcomes, publication details, study design and methodology, study population, and study interventions and comparators.

### Statistical methods

We conducted direct comparisons using random effect models and network meta-analyses using Bayesian statistical methods. Network meta-analyses included direct comparisons constructed with connections between treatments if there was a corresponding comparison between two drug categories in the articles, and indirect comparisons constructed with connections between all treatments using direct comparisons as links between categories.



**Figure 1** Systematic review flowchart. RCT, randomized controlled trial; DM2, diabetes mellitus 2.

Changes in HbA1c, weight and BMI were treated as continuous variables, calculated as between-group changes in mean values from baseline to follow-up, and presented as the difference-in-difference (DiD). A negative DiD implies the comparator is more successful than the reference agent. For example, in one study the SU cohort gained 1.2 kg while the DPP-4 cohort lost 1.5 kg from baseline (15). With DPP-4 as the comparator group, the DiD for weight would be -2.7 kg (e.g. DPP-4 s lead to greater weight loss). When the net change or the variances for change were not reported directly, we used confidence intervals (CIs) of changes to calculate variance. If only the variances or CIs at baseline and at the end of follow-up were available, we estimated variance by assuming the correlation coefficient was 0.5 between baseline and follow-up values (16). Achievement of HbA1c <7% and proportion of patients with any hypoglycaemic events treated as dichotomous variables and relative risk (RR) calculated to compare treatment groups.

For direct comparisons, separate analyses conducted for each outcome and each pair of drug classes using DerSimonian and Laird random effects model. Weighted mean

differences (WMDs) and associated 95% CIs reported. For dichotomous outcomes, RRs and associated 95% CIs reported instead. To assess heterogeneity, I2 index was used. I2 index can be interpreted as the percentage of the total variability in a set of values due to true heterogeneity. Percentages of around 25% (I<sup>2</sup> = 25), 50% (I<sup>2</sup> = 50) and 75% (I<sup>2</sup> = 75) would mean low, medium and high heterogeneity, respectively.

For network analyses, Bayesian Markov-chain Monte Carlo random effects models were constructed using the Bayesian software WinBUGS (17) with weakly informative priors. Pooled estimates from the posterior distribution and 95% credible intervals (CrIs) (Bayesian equivalent of CIs) reported. The lorcaserin RCT had more than one treatment arm containing the same therapy, and the analyses were adjusted by taking into account the correlation between arms.

To address the risk of bias within individual studies, we evaluated all studies using the Jadad score, a measure of study methodological quality with scoring range from 1 (very poor) to 5 (rigorous) (18), though no cutoff was set. Forest plots constructed for visualization of changes in

**Table 1** Direct meta-analysis: primary outcomes

Interpretation Comparison group	Reference group	Change in HbA1c*, %		Achieved HbA1c goal <7%		Change in weight†, kg		Change in BMI*, kg m <sup>-2</sup>		Overall hypoglycaemia	
		No.	WMD (95%CI)	No.	RR (95%CI)	No.	WMD (95%CI)	No.	WMD (95%CI)	No.	RR (95%CI)
Lorcaserin	Placebo	2	<b>-0.55 (-0.65 to -0.45)†</b>	2	<b>1.95 (1.61 to 2.35)†</b>	2	<b>-3.24 (-3.54 to -2.95)†</b>	2	<b>-1.05 (-1.15 to -0.95)†</b>	2	1.35 (0.83 to 2.21)‡
AGI	Placebo	2	<b>-0.81 (-1.12 to -0.51)‡</b>	1	<b>2.47 (1.36 to 4.48)</b>	1	-0.89 (-2.03 to 0.25)	1	0.50 (0.05 to 5.40)	1	0.50 (0.05 to 5.40)
Sulphonylurea	Placebo	2	<b>-0.67 (-1.00 to -0.34)†</b>	1		1	<b>1.34 (0.60 to 2.08)</b>	1	<b>0.46 (0.19 to 0.73)</b>	3	<b>2.80 (1.66 to 4.73)‡</b>
TZD	Placebo	3	<b>-0.90 (-1.30 to -0.51)†</b>	1	<b>1.66 (1.22 to 2.26)</b>	2	<b>2.30 (1.71 to 2.89)‡</b>	1	0.80 (-0.35 to 1.95)	2	0.83 (0.12 to 5.81)‡
DPP-4 inhibitor	Placebo	4	<b>-0.58 (-0.75 to -0.40)§</b>	5	<b>1.62 (1.36 to 1.92)‡</b>	2	0.09 (-0.36 to 0.55)§	1	-0.03 (-0.31 to 0.25)	6	1.09 (0.49 to 2.43)‡
Glimide	Placebo	.	.	.	.	1	<b>3.27 (1.87 to 4.67)</b>	.	.	.	.
SGLT-2 inhibitor	Placebo	.	.	.	.	1	<b>-2.08 (-2.85 to -1.31)</b>	.	.	1	0.67 (0.11 to 3.90)
TZD	Sulphonylurea	5	0.01 (-0.10 to 0.13)†	2	0.87 (0.70 to 1.08)‡	4	0.62 (-0.15 to 1.39)‡	4	0.07 (-0.25 to 0.39)†	5	<b>0.19 (0.10 to 0.35)§</b>
GLP-1 agonist	Sulphonylurea	3	0.10 (-0.21 to 0.42)†	1	<b>1.44 (1.22 to 1.70)</b>	3	<b>-6.83 (-11.14 to -2.51)†</b>	2	-2.90 (-5.64 to -0.15)†	3	<b>0.54 (0.48 to 0.62)‡</b>
DPP-4 inhibitor	Sulphonylurea	7	0.08 (-0.01 to 0.17)§	6	0.95 (0.90 to 1.00)†	5	<b>-2.00 (-2.45 to -1.56)†</b>	.	.	4	<b>0.14 (0.08 to 0.25)†</b>
Glimide	Sulphonylurea	1	0.08 (-0.08 to 0.24)	1	0.84 (0.62 to 1.15)	1	-0.49 (-1.33 to 0.35)	.	.	1	1.07 (0.58 to 1.97)
SGLT-2 inhibitor	Sulphonylurea	1	-0.11 (-0.19 to -0.03)	1	1.10 (0.94 to 1.28)	1	<b>-4.40 (-4.75 to -4.05)</b>	.	.	1	<b>0.08 (0.05 to 0.13)</b>
GLP-1 agonist	TZD	1	<b>-0.30 (-0.55 to -0.05)</b>	.	.	1	<b>-5.10 (-5.95 to -4.25)</b>	.	.	1	2.06 (0.19 to 22.52)
DPP-4 inhibitor	TZD	2	0.05 (-0.07 to 0.17)†	1	0.86 (0.34 to 2.19)	.	.	.	.	2	2.01 (0.64 to 6.24)‡
DPP-4 inhibitor	GLP-1 agonist	1	<b>0.60 (0.35 to 0.85)</b>	.	.	1	<b>1.50 (0.62 to 2.38)</b>	.	.	1	2.41 (0.47 to 12.24)

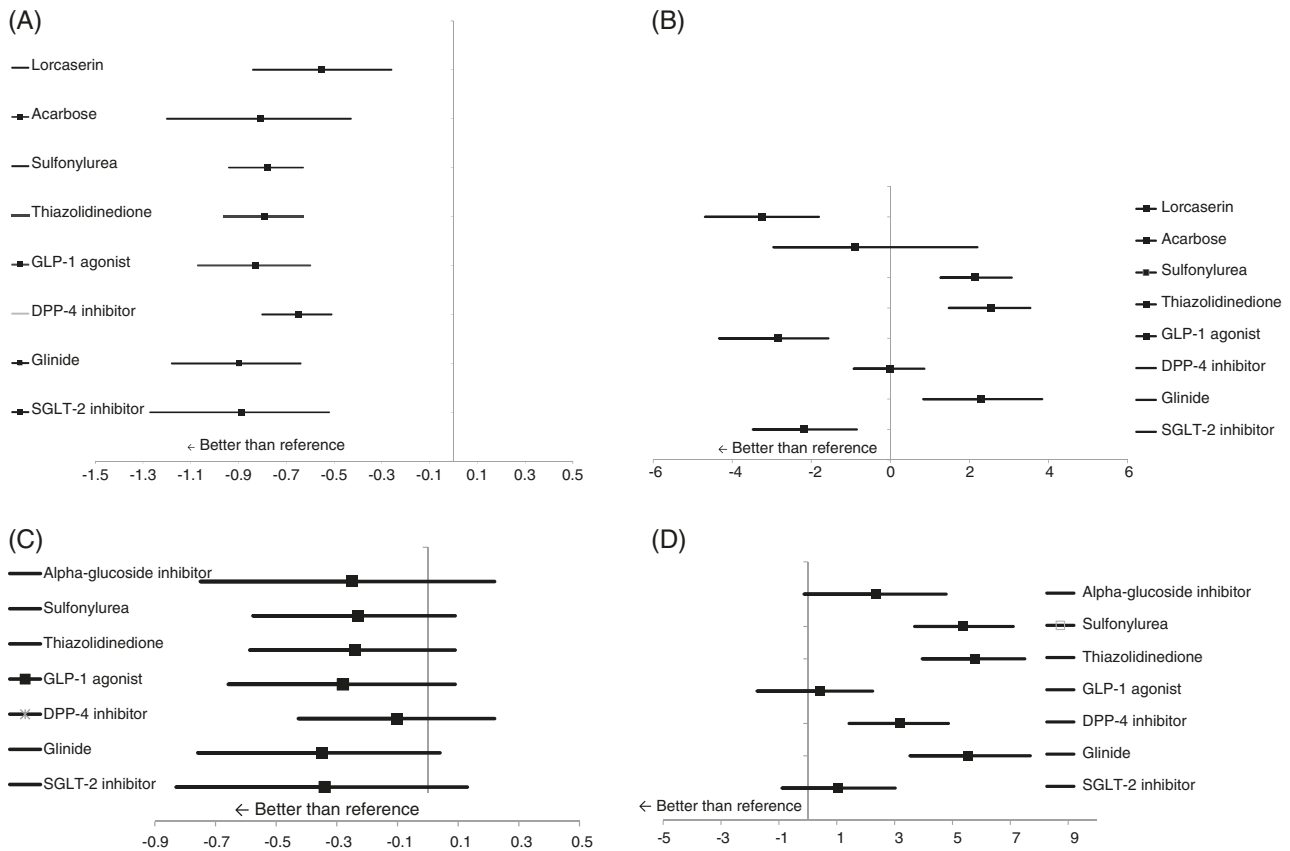
\*Changes in HbA1c, weight and BMI were calculated as the between-group changes in mean values from baseline to follow-up, and presented as the difference-in-difference (DID) in the results. Negative DIDs for weight, e.g. do not indicate that both reference and comparison groups 'lost' weight, rather that the difference of the weight change between the two cohorts was negative. In the case of interpreting weight loss, a negative DID implies the comparator is more successful than the reference agent. Conversely, positive DIDs do not indicate whether the reference or comparison groups gained weight, rather that the weight change from baseline to follow-up was significantly greater in the comparator arms than in the reference arms. If the goal is weight loss, a positive DID for weight implies the comparator is less successful than the reference agent.

†*P* > =75%.

‡*P* < 50%.

§50% ≤ *P* < 75%.

BMI, body mass index; CI, confidence interval; AGI, alpha-glucosidase inhibitor; TZD, thiazolidinedione; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2; HbA1c, haemoglobin A1c; WMD, weighted mean difference; RR, relative risk.



**Figure 2** (A) Percent change in HbA1c vs. placebo (95% CrI); (B) change in weight (kg) vs. placebo (95% CrI); (C) percent change in HbA1c vs. lorcaserin (95% CrI); (D) change in weight (kg) vs. lorcaserin (95% CrI). CrI, credible interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, haemoglobin A1c; SGLT-2, sodium-glucose cotransporter-2.

HbA1c and weight when considering all comparisons vs. placebo and vs. lorcaserin.

## Results

The initial search identified 6,552 articles. After title and abstract screening, 191 underwent full text review. Of these, 150 articles were excluded (124 did not meet intervention criteria, 9 not parallel-group RCTs, 9 duplicates, 3 compared same class of agents in each treatment arm, 2 had treatment periods less than 12 weeks, 2 were non-English and 1 reported medians). Grey literature searches did not identify additional articles. The 41 accepted articles (Fig. 1) represented all seven classes of glucose lowering agents and lorcaserin: 23 studies of SU (15,19–40), 18 of DPP-4 inhibitors (15,19,21,22,24,25,29–31,41–49), 14 of TZDs (27,32–34,36,37,39,42,45–48,50,51), 4 of GLP-1 agonists (23,26,28,45), 3 of glinides (35,52,53), 3 of AGIs (54–56), 2 of SGLT-2 inhibitors (20,57) and 1 of lorcaserin (12). Five of the seven glucose lowering agent classes were represented by at least two different agents, while AGIs were represented by acarbose only and GLP-1 agonists by exenatide only.

Study sizes ranged from 14 to over 1700 patients per arm. Mean age ranged from 49 to 64 years, and mean duration of T2DM ranged from 4.1 to 9.5 years. Of the 41 studies, 31 had a Jadad scores of at least 3, indicative of reasonably high methodological quality. Industry support was disclosed in 29. All 41 accepted studies included baseline HbA1c measurements, 40 included baseline fasting glucose. 40 reported baseline BMI; 30 weight; 32 provided data on hypoglycaemic events. There were 15 meta-analyzable direct comparisons for the primary outcomes. Seven agents were directly compared against placebo for at least one outcome, 5 against SUs, 2 against TZDs and 1 against GLP-1 agonists. Using these direct comparisons, there were 36 analyzable network comparisons across 9 therapies (7 glucose lowering medications, lorcaserin and placebo).

In direct comparisons, the percent reduction [% (95% CI)] in HbA1c (from baseline to study end) in patients taking lorcaserin [-0.55 (-0.65, -0.45)], AGIs [-0.81 (-1.12, -0.51)], SUs [-0.67 (-1.00, -0.34)], TZDs [-0.90 (-1.30, -0.51)] and DPP-4 inhibitors [-0.58 (-0.75, -0.40)] was statistically significantly greater in treatment groups vs. placebo. The HbA1c reduction in patients taking GLP-

**Table 2** Network meta-analysis: key outcomes

Comparison group Interpretation	Change in HbA1c*, % Difference (95% CrI) Negative and CrI does not include 0 → better than reference	Achieved HbA1c goal <7% RR (95%CrI) Above 1 and CrI does not include 1 → better than reference	Change in Weight*, kg Difference (95% CrI) Negative and CrI does not include 0 → better than reference	Change in BMI*, kg m <sup>-2</sup> Difference (95% CrI) Negative and CrI does not include 0 → better than reference	Overall Hypoglycaemia RR (95%CrI) Above 1 and CrI does not include 1 → greater than reference
Reference: placebo					
Lorcaserin	<b>-0.55 (-0.84, -0.26)</b>	<b>2.38 (1.68 to 3.30)</b>	<b>-3.24 (-4.66, -1.81)</b>	-1.06 (-2.76, 0.64)	1.46 (0.45 to 3.28)
AGI	<b>-0.81 (-1.20, -0.43)</b>	<b>2.81 (1.43 to 4.89)</b>	-0.89 (-2.87, 1.10)	n/a	0.82 (0.01 to 3.94)
Sulphonylurea	<b>-0.78 (-0.94, -0.63)</b>	<b>2.33 (1.82 to 3.01)</b>	<b>2.14 (1.29, 3.07)</b>	0.56 (-0.74, 1.86)	<b>4.00 (2.47 to 6.30)</b>
TZD	<b>-0.79 (-0.96, -0.63)</b>	<b>2.06 (1.50 to 2.83)</b>	<b>2.55 (1.50, 3.54)</b>	0.63 (-0.80, 2.12)	0.69 (0.29 to 1.32)
GLP-1 agonist	<b>-0.83 (-1.07, -0.60)</b>	<b>3.44 (2.35 to 4.98)</b>	<b>-2.83 (-4.31, -1.57)</b>	<b>-2.33 (-4.25, -0.38)</b>	1.35 (0.44 to 2.86)
DPP-4 inhibitor	<b>-0.65 (-0.80, -0.51)</b>	<b>2.12 (1.69 to 2.66)</b>	-0.04 (-0.97, 0.86)	0.004 (-1.42, 1.45)	1.05 (0.55 to 1.83)
Glinide	<b>-0.90 (-1.18, -0.64)</b>	<b>1.90 (1.09 to 3.08)</b>	<b>2.30 (0.87, 3.84)</b>	n/a	<b>4.02 (1.96 to 7.32)</b>
SGLT-2 inhibitor	<b>-0.89 (-1.27, -0.52)</b>	<b>2.57 (1.82 to 3.64)</b>	<b>-2.18 (-3.45, -0.85)</b>	n/a	0.57 (0.16 to 1.46)
Reference: lorcaserin					
AGI	-0.26 (-0.75, 0.21)	1.21 (0.58 to 2.14)	2.35 (-0.08, 4.78)	n/a	0.73 (0.01 to 3.88)
Sulphonylurea	-0.23 (-0.57, 0.09)	1.00 (0.69 to 1.45)	<b>5.38 (3.73, 7.10)</b>	1.61 (-0.51, 3.77)	<b>3.51 (1.12 to 9.67)</b>
TZD	-0.24 (-0.58, 0.09)	0.89 (0.57 to 1.34)	<b>5.79 (3.99, 7.50)</b>	1.68 (-0.54, 3.96)	0.60 (0.14 to 1.78)
GLP-1 agonist	-0.28 (-0.65, 0.09)	1.48 (0.97 to 2.27)	0.41 (-1.72, 2.24)	-1.27 (-3.83, 1.29)	1.19 (0.23 to 3.64)
DPP-4 inhibitor	-0.10 (-0.42, 0.22)	0.91 (0.63 to 1.30)	<b>3.20 (1.46, 4.86)</b>	1.06 (-1.19, 3.30)	0.93 (0.26 to 2.67)
Glinide	-0.35 (-0.75, 0.04)	0.82 (0.42 to 1.41)	<b>5.54 (3.58, 7.69)</b>	n/a	3.54 (0.98 to 10.25)
SGLT-2 inhibitor	-0.34 (-0.82, 0.13)	1.11 (0.71 to 1.70)	1.06 (-0.85, 3.02)	n/a	0.51 (0.09 to 1.78)

Bold values represent RR ≠ 1 or difference ≠ 0 with significance level = 0.05.

\*Changes in HbA1c, weight and BMI were calculated as the between-group changes in mean values from baseline to follow-up, and presented as the difference-in-difference (DiD) in the results. Negative DiDs for weight, for example, do not indicate that both reference and comparison groups "lost" weight, rather that the difference of the weight change between the two cohorts was negative. In the case of interpreting weight loss, a negative DiD implies the comparator is more successful than the reference agent. Conversely, positive DiDs do not indicate whether the reference or comparison groups gained weight, rather that the weight change from baseline to follow-up was significantly greater in the comparator arms than in the reference arms. If the goal is weight loss, a positive DiD for weight implies the comparator is less successful than the reference agent.

BMI, body mass index; CrI, credible interval; AGI, alpha-glucoside inhibitor; TZD, thiazolidinedione; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2; HbA1c, haemoglobin A1c; RR, relative risk.

1 agonists was statistically significantly greater than the reduction seen in patients taking TZDs [-0.30(-0.55 to -0.05)] and DPP-4 [0.60(0.35 to 0.85)] inhibitors. DiD for weight was positive for users of SUs [kg difference(95% CI): 1.34(0.60 to 2.08)], TZDs [kg difference(95% CI): 2.30(1.71 to 2.89)] and glinides [kg difference (95% CI): 3.27(1.87 to 4.67)] vs. patients receiving placebo. If the goal is weight loss, a positive DiD for weight implies the comparator is less successful than the reference agent. DiD for weight was negative in users of lorcaserin (who lost weight) [kg difference(95% CI): -3.24(-3.54,-2.95)] and SGLT-2 users [-2.08(-2.85, -1.31)] vs. in placebo (Table 1). That is, lorcaserin and SGLT-2s were more successful than the reference agent (Fig. 2).

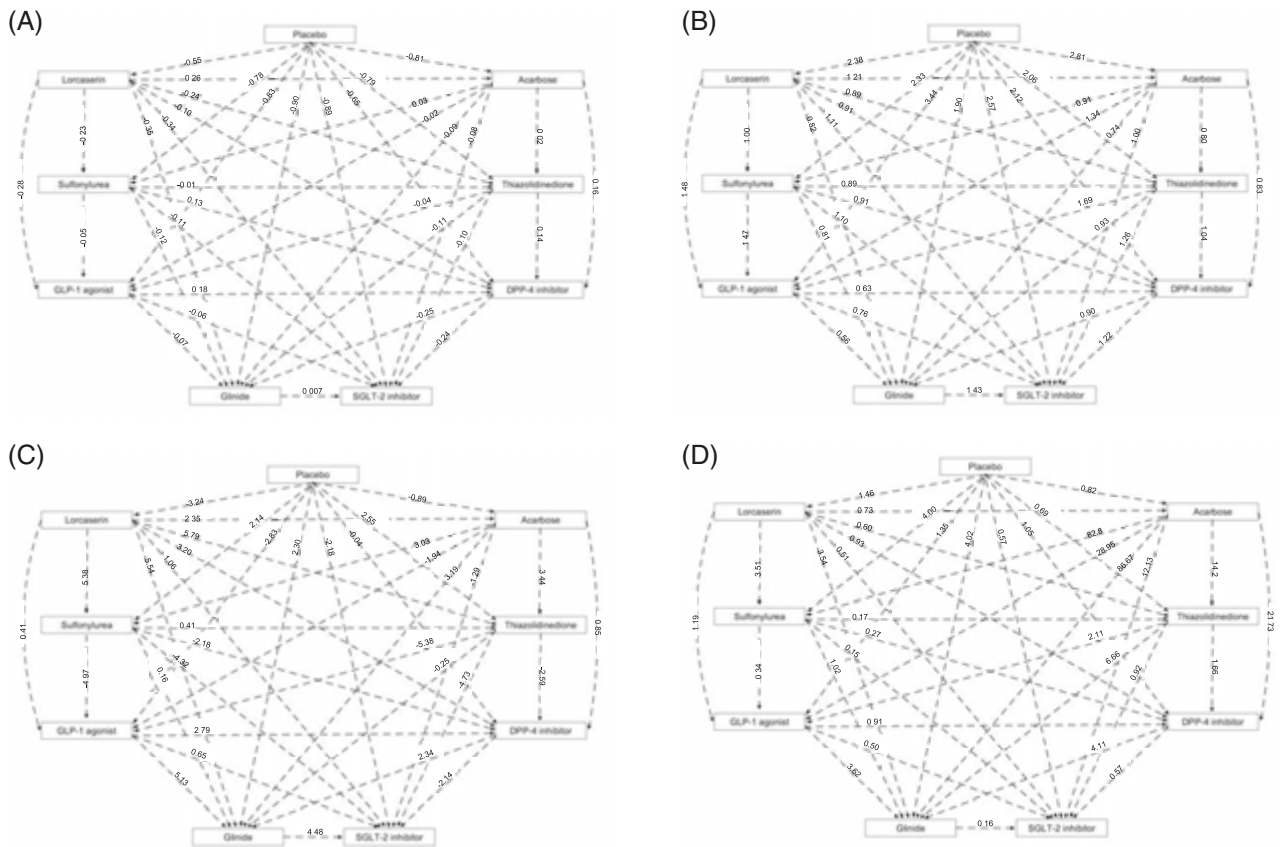
In network meta-analyses, lorcaserin reduced HbA1c by 0.55% more (95% CrI:-0.84, -0.26) compared to placebo and was 2.38 times more likely (95% CrI:1.68, 3.30) to lead to HbA1c <7% compared to placebo. None of the other glucose lowering agents were statistically significantly different from lorcaserin in HbA1c reduction or achievement of HbA1c <7%. Hypoglycaemia risk was not significantly different for any studied agent except SUs were

associated with higher risk of hypoglycaemia than lorcaserin [RR(95% CrI): 3.51(1.12, 9.67)] (Table 2, Fig. 3).

DiD for weight in users of TZDs, glinides, SUs and DPP-4 inhibitors was positive vs. in users of lorcaserin (who lost weight) {[kg difference(95% CrI): TZDs [5.79(3.99, 7.50)], glinides [5.54(3.58, 7.69)], SUs [5.38(3.73, 7.10)] and DPP-4 inhibitors [3.20(1.46, 4.86)]}. There was no statistically significant DiD for weight between lorcaserin and AGIs, GLP-1 agonists and SGLT-2 inhibitors {[kg difference(95% CrI): AGI [2.35(-0.08, 4.78)], GLP-1 [0.41 (-1.72, 2.24)] and SGLT-2 [1.06(-0.85, 3.02)]} (Table 2 and Fig. 3).

## Discussion

This systematic review and network meta-analysis provide preliminary evidence to support consideration of lorcaserin as an alternative to second-line glucose lowering therapies in patients with a BMI ≥27 kg m<sup>-2</sup>. Although additional studies are needed, this analysis suggests that lorcaserin may perform favourably as an adjunct to current glucose lowering agents. In direct analyses, lorcaserin, AGIs, SUs, TZDs and DPP-4 inhibitors were all significantly more



**Figure 3** (A) Network comparison: change in HbA1c, % difference; (B) network comparison: achieved HbA1c goal <7% RR; (C) network comparison: change in weight, kg difference; (D) network comparison: overall hypoglycaemia RR. RR, relative risk; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, haemoglobin A1c; SGLT-2, sodium-glucose cotransporter-2.

effective than placebo at reducing HbA1c and at bringing HbA1c to <7%. Lorcaserin and SGLT-2 reduced weight significantly more than placebo. In network analyses, lorcaserin also resulted in negative DiD for weight vs. TZDs, glinides, SUs and DPP-4 inhibitors (i.e. lorcaserin was more successful in terms of weight loss goals). None of the glucose lowering agents were statistically superior to lorcaserin at reducing HbA1c or achieving HbA1c goal. The network meta-analysis also demonstrated that lorcaserin, GLP-1 agonists and SGLT-2 inhibitors all reduced weight by a statistically significant amount vs. placebo.

Two-thirds of Americans with diabetes are obese, a condition exacerbated by glucose lowering medication-related weight gain, which in turn may hinder glycaemic control (2,8). Obesity increases the risk of other comorbidities, including cardiovascular disease (58). This highlights the need to consider glucose lowering regimens not associated with weight gain, which instead complement lifestyle changes and produce weight loss. The findings of reduced weight and similar HbA1c improvements with lorcaserin are important. SU, TZD and glinides significantly increased weight vs. placebo, results which are consistent with existing literature (5,59). SU, TZD, DPP-4 inhibitors and

glinides all had less favourable weight outcomes compared to lorcaserin.

The main strengths of this study are rigour of the search, breadth of information, and use of network meta-analysis. The search covered 15 years of glucose lowering RCT literature with more than 6000 articles screened. Unlike traditional 2-intervention meta-analyses, this study combined eight different interventions plus placebo, and standardized the outcomes reported such that all regimens could be compared.

The study has important limitations. The inclusion criteria for lorcaserin RCTs differed from those for other trials, resulting in conceptual heterogeneity among included articles. Conceptual heterogeneity may increase error associated with cross-study comparisons. At the time of our study, there was only one lorcaserin RCT with T2DM patients. Applying the same criteria to lorcaserin as to the other trials would have prevented any lorcaserin comparisons. Second, while there were two approved GLP-1 agonists at the time of the study, only exenatide studies were included. We identified and appropriately excluded 11 liraglutide trials (five because patients had not failed metformin monotherapy, three because liraglutide was not the second glucose lowering medication, two because no

primary outcomes of interest were reported and one because patients used basal insulin). In the current study, GLP-1 agonists were associated with statistically significant weight and BMI reduction compared to placebo, although the effects were not different than those observed with lorcaserin. As weight loss has been observed with liraglutide (60), exclusion of these studies may have resulted in an inaccurate estimation of the weight-related effects of GLP-1 agonists as a category. Third, the network meta-analysis relied on many indirect comparisons between the nine nodes. Using indirect, rather than direct, comparisons widened CIs and may have led to missed true differences between treatments. Fourth, while 31 of 41 articles had Jadad scores of at least 3, 10 with lower scores were still included. The poorer methodological qualities in those 10 may have affected overall quality of the network meta-analysis.

## Conclusions

The current network meta-analysis suggests that lorcaserin may be non-inferior to the studied glucose lowering agents at lowering overall HbA1c and at reducing HbA1c to <7%. Treatment with lorcaserin resulted in statistically significantly less hypoglycaemia than SU and was similar to other glucose lowering agents and to placebo in regards to hypoglycaemia. In addition to its potential glucose lowering qualities, lorcaserin improved weight outcomes compared to SU, TZD, DPP-4 inhibitors and glinides. Additional research is needed as the current analysis included only one study of lorcaserin; however, our analysis suggests that in patients with BMI  $\geq 27$  kg m<sup>-2</sup> who do not achieve glycaemic control on a single agent, lorcaserin may be considered an alternative to an add-on glucose lowering medication.

## Conflict of Interest Statement

Research was supported by Eisai, Inc. LN is a consultant for Eisai. MB, DB, EC and EP are employees of Partnership for Health Analytic Research, LLC, which was paid by Eisai to conduct this research. ZW is an employee of Eisai.

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