Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

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Summary

Background Combination treatment with a glucagon-like peptide-1 (GLP-1) agonist and basal insulin has been proposed as a treatment strategy for type 2 diabetes that could provide robust glucose-lowering capability with low risk of hypoglycaemia or weight gain. We thus did a systematic review and meta-analysis of randomised controlled trials to assess the effect of this combination treatment on glycaemic control, hypoglycaemia, and weight gain in patients with type 2 diabetes.

Methods We systematically searched PubMed, Embase, Cochrane, Web of Knowledge, FDA.gov, and ClinicalTrials.gov for randomised controlled trials (published between Jan 1, 1950, and July 29, 2014; no language restrictions) comparing GLP-1 agonist and basal insulin combination treatment to other anti-diabetic treatments. Our main endpoints were glycaemic control, hypoglycaemia, and change in weight. We assessed pooled data by use of a random-effects model.

Findings Of 2905 identified studies, 15 were eligible and were included in our analysis (N=4348 participants). Compared with other anti-diabetic treatments, GLP-1 agonist and basal insulin combination treatment yielded an improved mean reduction in glycated haemoglobin (HbA_{1c}) of –0·44% (95% CI –0·60 to –0·29), an improved likelihood of achieving the target HbA_{1c} of 7·0% or lower (relative risk [RR] 1·92; 95% CI 1·43 to 2·56), no increased relative risk of hypoglycaemia (0·99; 0·76 to 1·29), and a mean reduction in weight of –3·22 kg (–4·90 to –1·54). Furthermore, compared with basal-bolus insulin regimens, the combination treatment yielded a mean reduction in HbA_{1c} of –0·1% (–0·17 to –0·02), with lower relative risk of hypoglycaemia (0·67, 0·56 to 0·80), and reduction in mean weight (–5·66 kg; –9·8 to –1·51).

Interpretation GLP-1 agonist and basal insulin combination treatment can enable achievement of the ideal trifecta in diabetic treatment: robust glycaemic control with no increased hypoglycaemia or weight gain. This combination is thus a potential therapeutic strategy that could improve the management of patients with type 2 diabetes.

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Introduction

Type 2 diabetes mellitus is a chronic disorder characterised by progressive deterioration of the pancreatic β cells that synthesise and secrete insulin, resulting in worsening hyperglycaemia over time.[1] Available anti-diabetic treatments have not been shown to reliably alter this natural history of deteriorating β-cell function.[2,3] As such, the typical clinical course of type 2 diabetes involves the sequential addition of anti-diabetic drugs over time, followed eventually by basal insulin treatment before more complex treatment regimens with the addition of prandial or bolus insulin.[4] Basal-bolus regimens, in which patients take basal insulin once or twice a day and bolus insulin before each meal, are typically the last line in this therapeutic progression. Even with intensive basal-bolus insulin treatment, however, the achievement of glycaemic targets in practice is often limited by inadequate insulin dose titration, owing to concerns about the risks of hypoglycaemia and weight gain.[4] Indeed, an ideal anti-diabetic treatment would be one that can couple the achievement of glycaemic control with a low propensity for causing hypoglycaemia and weight gain.

Glucagon-like peptide-1 (GLP-1) agonists are a novel class of injectable anti-diabetic drugs that can improve glycaemic control and induce weight loss.[5] In clinical practice, approved GLP-1 agonists are widely used as second-line or third-line agents after the failure of one or more oral anti-diabetic drugs.[6,7] However, their optimal role in the clinical management of type 2 diabetes has not been established.

In this context, there is much interest in the potential benefits of combination treatment consisting of a GLP-1 agonist and basal insulin—strong physiological and clinical rationale lend support to such a strategy.[8,9] First, this combination offers the potential for robust glucose-lowering, owing to the complementary effects of its components. Specifically, while basal insulin can target fasting and post-absorptive glucose control, GLP-1 agonists can reduce postprandial glycaemic excursion through the inhibition of gastric emptying, stimulation of glucose-dependent insulin secretion, and suppression of hyperglucagonaemia.[7] Second, their low hypoglycaemic potential suggests that GLP-1 agonists are less likely than bolus insulin to cause hypoglycaemia when combined with basal insulin. Third, the weight-lowering effect of a

GLP-1 agonist might limit the weight gain associated with insulin. Finally, this combination might allow insulin dosage to be reduced, which could further lower the risks of hypoglycaemia and weight gain.

In view of this compelling rationale, a series of clinical trials have assessed GLP-1 agonist and basal insulin combination treatment versus a variety of anti-diabetic treatments, including basal-bolus insulin regimens. Recognising that individual studies might not be able to provide sufficient data on their own to affect practice, we sought to objectively assess the potential role of this treatment in the management of type 2 diabetes. We therefore did a systematic review and meta-analysis of randomised controlled trials to establish the effect of GLP-1 agonist and basal insulin combination treatment on the key outcomes of glycaemic control, hypoglycaemia, and weight regulation in patients with type 2 diabetes.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews (number CRD42014010688).[10]

We selected relevant studies published between Jan 1, 1950, and July 29, 2014, by searching Embase, PubMed, Cochrane, Web of Knowledge, FDA.gov, and ClinicalTrials.gov. We applied no language restrictions. We used the following combined text and MeSH terms: "insulin" and "glucagon-like peptide 1 receptor agonist". The complete search used for PubMed was: (insulin [MeSH Terms] OR insulin [Text Word] OR NPH [Text word] OR glargine [Text word] OR detemir [Text word] OR degludec [Text word]) AND (glucagon-like peptide 1 receptor agonist [Text Word] OR exenatide [Text word] OR liraglutide [Text word] OR lixisenatide [Text word] OR dulaglutide [Text word] OR albiglutide [Text word] OR semaglutide [Text word] OR taspoglutide (Text word])). We considered all potentially eligible studies for review, irrespective of the primary outcome or language. We also did a manual search, using the reference lists of key articles published in English.

Study selection and data extraction

We regarded studies as eligible for inclusion if they were randomised clinical trials done in adults with type 2 diabetes, compared GLP-1 agonist and basal insulin combination treatment to another treatment strategy, had at least 8 weeks' duration of intervention, and reported changes in glycated haemoglobin (HbA$_{1c}$) or the proportion of participants with an HbA$_{1c}$ of 7·0% or lower at the end of the intervention period or the number of participants with any hypoglycaemic episode. Exclusion criteria were as follows: observational and retrospective studies; studies with less than 8 weeks duration of intervention, and studies that did not assess GLP-1 agonist and basal insulin combination treatment.

We compared combination treatment consisting of a GLP-1 agonist and basal insulin to any other anti-diabetic treatment strategy, with no restriction on treatment history. The outcomes assessed were as follows: change in HbA$_{1c}$ between baseline and end of intervention, proportion of participants achieving an HbA$_{1c}$ of 7·0% or lower at the end of intervention, number of participants with any hypoglycaemic episode, and change in weight between baseline and end of intervention.

Two independent investigators (CE, RR) reviewed study titles and abstracts, and studies that satisfied the inclusion criteria were retrieved for full-text assessment. Trials selected for detailed analysis and data extraction were analysed by two investigators (CE and RR) with an agreement value (κ) of 96·5%; disagreements were resolved by a third investigator (CK).

We extracted the following data from each selected study: total number of participants, age, sex, trial duration, anti-diabetic treatments, change in HbA$_{1c}$ (mean [SD]); number of participants achieving an HbA$_{1c}$ of 7·0% or lower at the end of the intervention, change in body weight (mean [SD]); and number of participants with any hypoglycaemic episodes. We used imputed data for obtaining the SD of HbA$_{1c}$ change for one study reported in abstract form.[11] Two independent reviewers (CE, CK) assessed risk for bias according to the PRISMA recommendations.

Statistical analysis

We assessed the effect of GLP-1 and basal insulin combination treatment on four outcomes: glycaemic control, as assessed by both HbA$_{1c}$ and achievement of
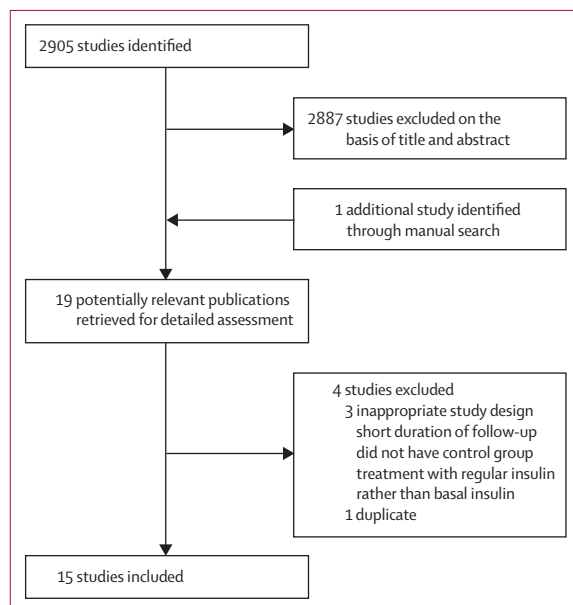

Figure 1: Study selection process

target HbA$_{1c}$ of 7·0% or lower, incidence of any hypoglycaemia, and weight. We analysed HbA$_{1c}$ and weight as continuous variables and reported absolute differences between arithmetic means before and after interventions. For analyses of the proportion of participants achieving an HbA$_{1c}$ of 7·0% or lower and those having any episode of hypoglycaemia, we calculated an overall relative risk (RR).
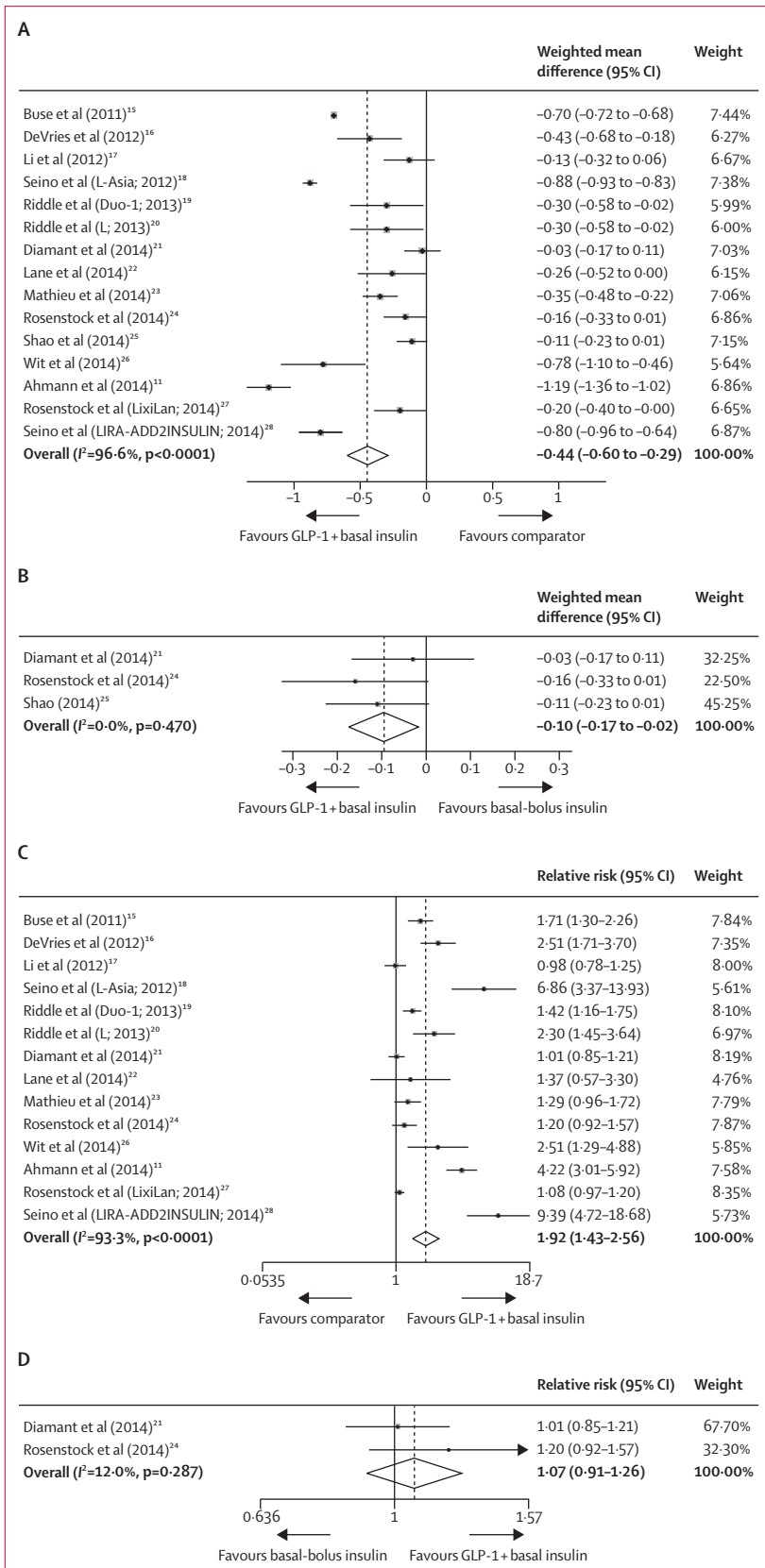
We calculated pooled estimates of the mean differences in HbA$_{1c}$ and weight between intervention groups by using a random-effects model (DerSimonian–Laird method) to

adequately account for the additional uncertainty associated with inter-study variability in the effect of different anti-diabetic drugs. For categorical outcomes, we also calculated pooled estimates of the relative risk with a random-effects model. In the meta-analyses of each outcome, we did pre-planned sensitivity analyses restricted to trials that compared GLP-1 agonist and basal insulin combination treatment to basal-bolus insulin regimens. This comparison is the most important clinical question pertaining to the role of GLP-1 agonist and basal insulin

	Year	Background treatment in both study groups	Differential interventions in study groups	Duration of interventions	N	Number of men	Mean age	Mean baseline HbA$_{1c}$	Mean body-mass index (kg/m^2)	Mean baseline weight (kg)	Mean duration of diabetes
Buse et al[15]	2011	Glargine ± metformin, pioglitazone, or both	Exenatide vs placebo	30 weeks	259	148 (57%)	59 years	8·4%	33·5	94·4	12 years
DeVries et al[16]	2012	Metformin and liraglutide	Detemir vs no detemir	26 weeks (after 12 week liraglutide run-in phase)	323	177 (55%)	57 years	8·2%	34·4	95·7	8·6 years
Li et al[17]	2012	Basal insulin or premixed insulin ± metformin, sulfonylurea, thiazolidinedione, glinide, α-glucosidase inhibitor	Liraglutide vs no liraglutide	12 weeks	84	50 (60%)	52 years	8·7%	30·35	87·5	9·2 years
Seino et al (GetGoal-L-Asia)[18]	2012	Basal insulin ± sulfonylurea	Lixisenatide vs placebo	24 weeks	311	149 (48%)	58·3 years	8·5%	25·2	65·8	13·9 years
Riddle et al (GetGoal-Duo 1)[19]	2013	Glargine plus metformin ± thiazolidinedione	Lixisenatide vs placebo	24 weeks (after 12 week titration of glargine)	446	222 (50%)	56 years	7·6%	31·8	87	9·2 years
Riddle et al (GetGoal-L)[20]	2013	Basal insulin ± metformin	Lixisenatide vs placebo	24 weeks	495	228 (46%)	57 years	8·4%	32·1	87·7	12·5 years
Diamant et al[21]	2014	Glargine plus metformin	Exenatide vs lispro (with each meal)	30 weeks (after 12 week titration of glargine)	510	261 (51%)	59·4 years	8·2%	32·5	90·2	11·48 years
Lane et al[22]	2014	CSII or MDI ± metformin	Liraglutide vs no liraglutide	24 weeks	37	17 (46%)	59·7 years	7·8%	39·6	120	17·1 years
Mathieu et al[23]	2014	Degludec plus metformin	Liraglutide vs insulin aspart (with largest daily meal)	28 weeks	177	116 (66%)	61 years	7·7%	32·2	93·3	12·3 years
Rosenstock et al[24]	2014	Glargine ± metformin, pioglitazone, or both	Albiglutide weekly vs lispro (with each meal)	26 weeks (after 4–8 week titration of glargine)	566	268 (47%)	55·5 years	8·5%	Not available	92·1	11 years
Shao et al[25]	2014	Glargine	Exenatide vs insulin aspart (with each meal)	12 weeks	60	29 (48%)	42·5 years	7·6%	30·4	85·9	Newly diagnosed
De Wit et al[26]	2014	Basal insulin ± bolus insulin or metformin, sulfonylurea, or both	Liraglutide vs no liraglutide	26 weeks	50	31 (62%)	58 years	7·4%	33	100·1	7·9 years
Ahmann et al[31]	2014	Basal insulin ± metformin	Liraglutide vs placebo	26 weeks	450	Not available	Not available	8·2%	32·2	Not available	12·1 years
Rosenstock et al (LixiLan)[27]	2014	Metformin	Lixisenatide/glargine fixed combination vs glargine	24 weeks	323	Not available	Not available	8·0%	32·1	Not available	6·7 years
Seino et al (LIRA-ADD2INSULIN)[28]	2014	Insulin (basal, premixed, basal-bolus)	Liraglutide vs placebo	36 weeks	257	144 (56%)	60·5 years	8·8%	25·6	66·8	Not available

CSII=continuous subcutaneous insulin infusion. MDI=multiple daily insulin injections. HbA$_{1c}$=glycated haemoglobin.

Table 1: Characteristics of included studies

A

	Weighted mean difference (95% CI)	Weight
Buse et al (2011)[15]	–0·70 (–0·72 to –0·68)	7·44%
DeVries et al (2012)[16]	–0·43 (–0·68 to –0·18)	6·27%
Li et al (2012)[17]	–0·13 (–0·32 to 0·06)	6·67%
Seino et al (L-Asia; 2012)[18]	–0·88 (–0·93 to –0·83)	7·38%
Riddle et al (Duo-1; 2013)[19]	–0·30 (–0·58 to –0·02)	5·99%
Riddle et al (L; 2013)[20]	–0·30 (–0·58 to –0·02)	6·00%
Diamant et al (2014)[21]	–0·03 (–0·17 to 0·11)	7·03%
Lane et al (2014)[22]	–0·26 (–0·52 to 0·00)	6·15%
Mathieu et al (2014)[23]	–0·35 (–0·48 to –0·22)	7·06%
Rosenstock et al (2014)[24]	–0·16 (–0·33 to 0·01)	6·86%
Shao et al (2014)[25]	–0·11 (–0·23 to 0·01)	7·15%
Wit et al (2014)[26]	–0·78 (–1·10 to –0·46)	5·64%
Ahmann et al (2014)[11]	–1·19 (–1·36 to –1·02)	6·86%
Rosenstock et al (LixiLan; 2014)[27]	–0·20 (–0·40 to –0·00)	6·65%
Seino et al (LIRA-ADD2INSULIN; 2014)[28]	–0·80 (–0·96 to –0·64)	6·87%
Overall (I^2=96·6%, p<0·0001)	–0·44 (–0·60 to –0·29)	100·00%

Favours GLP-1 + basal insulin ← | → Favours comparator

B

	Weighted mean difference (95% CI)	Weight
Diamant et al (2014)[21]	–0·03 (–0·17 to 0·11)	32·25%
Rosenstock et al (2014)[24]	–0·16 (–0·33 to 0·01)	22·50%
Shao (2014)[25]	–0·11 (–0·23 to 0·01)	45·25%
Overall (I^2=0·0%, p=0·470)	–0·10 (–0·17 to –0·02)	100·00%

Favours GLP-1 + basal insulin ← | → Favours basal-bolus insulin

C

	Relative risk (95% CI)	Weight
Buse et al (2011)[15]	1·71 (1·30–2·26)	7·84%
DeVries et al (2012)[16]	2·51 (1·71–3·70)	7·35%
Li et al (2012)[17]	0·98 (0·78–1·25)	8·00%
Seino et al (L-Asia; 2012)[18]	6·86 (3·37–13·93)	5·61%
Riddle et al (Duo-1; 2013)[19]	1·42 (1·16–1·75)	8·10%
Riddle et al (L; 2013)[20]	2·30 (1·45–3·64)	6·97%
Diamant et al (2014)[21]	1·01 (0·85–1·21)	8·19%
Lane et al (2014)[22]	1·37 (0·57–3·30)	4·76%
Mathieu et al (2014)[23]	1·29 (0·96–1·72)	7·79%
Rosenstock et al (2014)[24]	1·20 (0·92–1·57)	7·87%
Wit et al (2014)[26]	2·51 (1·29–4·88)	5·85%
Ahmann et al (2014)[11]	4·22 (3·01–5·92)	7·58%
Rosenstock et al (LixiLan; 2014)[27]	1·08 (0·97–1·20)	8·35%
Seino et al (LIRA-ADD2INSULIN; 2014)[28]	9·39 (4·72–18·68)	5·73%
Overall (I^2=93·3%, p<0·0001)	1·92 (1·43–2·56)	100·00%

Favours comparator ← | → Favours GLP-1 + basal insulin

D

	Relative risk (95% CI)	Weight
Diamant et al (2014)[21]	1·01 (0·85–1·21)	67·70%
Rosenstock et al (2014)[24]	1·20 (0·92–1·57)	32·30%
Overall (I^2=12·0%, p=0·287)	1·07 (0·91–1·26)	100·00%

Favours basal-bolus insulin ← | → Favours GLP-1 + basal insulin

Figure 2: **Meta-analyses of glucagon-like peptide-1 (GLP-1) agonist and basal insulin combination treatment versus other anti-diabetic treatments, comparing HbA$_{1c}$ concentrations**

Outcomes assessed are: (A) HbA$_{1c}$ (%), (B) HbA$_{1c}$ (%) in studies that compared combination treatment with basal-bolus insulin treatment, (C) proportion of participants with HbA$_{1c}$ ≤7·0% at the end of intervention, and (D) proportion of participants with HbA$_{1c}$ ≤7·0% at the end of intervention in studies that compared combination treatment with basal-bolus insulin treatment. For each estimate, the grey shaded area is the weight of the estimate in proportion to the overall effect.

combination treatment and also reduced the heterogeneity of the treatment-induced changes in outcomes in the comparator arm seen in the overall analysis.

We assessed the possibility of publication bias by constructing a funnel plot of each trial's effect size against the standard error (appendix). We assessed funnel plot asymmetry using Begg and Egger tests, and defined significant publication bias as a p value <0·1. The trim-and-fill computation was used to estimate the effect of publication bias on the interpretation of the results.[12] We used the Cochran Q test to assess heterogeneity between studies.[13] We also did I^2 testing to assess the magnitude of the heterogeneity between studies, with values greater than 50% regarded as being indicative of moderate-to-high heterogeneity.[14] We used Stata (version 11.0) for all statistical analyses.

Role of the funding source

Results
We identified 2905 studies, of which 15 (with data for 4348 participants) were included in our analysis (figure 1). The 15 trials were all published between 2011 and 2014 (nine were published in 2014) (table 1).[11,15–28] Mean trial duration was 24·8 weeks (range 12 weeks to 36 weeks). Patients had mean baseline HbA$_{1c}$ of 8·13% (range 7·4–8·8), mean baseline body-mass index of 32·9 kg/m² (25·2–39·6), and mean duration of diabetes of 12·2 years (7·9–17·1). Six trials compared GLP-1 agonist with placebo on a background of basal insulin with or without oral anti-diabetic drugs;[11,15,18–20,28] three trials compared patients with or without GLP-1 agonist on a background of insulin (basal insulin alone or with bolus insulin) with or without oral anti-diabetic drugs;[17,22,26] and one study compared basal insulin with no basal insulin on a background of GLP-1 agonist with metformin.[16] One trial compared the combination treatment to basal insulin plus a single daily injection of bolus insulin[23] and one compared pre-mixed GLP-1 agonist plus basal insulin (LixiLan) versus placebo on a background of metformin.[28] Three trials compared basal insulin and GLP-1 agonist

combination treatment versus intensive basal-bolus insulin regimens,[21,24,25] a comparison of particular clinical interest and hence a pre-specified sensitivity analysis in our study. The appendix gives details of the algorithms for insulin dose titration used in the trials.

The appendix also shows the assessment of risk of bias in the trials. All 15 randomised controlled trials reported adequate randomisation, none was stopped early, and 12 were multicentre. However, eight studies[16,17,21,23–27] did not specify whether data collectors and outcome assessors were masked to treatment allocation and only two were not funded by industry.[17,22]

In a pooled analysis of all 15 trials, the combination of GLP-1 agonist and basal insulin led to a mean greater reduction in HbA_{1c} than with any other treatment strategy, with statistically significant between-study heterogeneity (figure 2). In this analysis there was publication bias on Egger test (p=0·0047; appendix). However, further analysis with trim-and-fill test indicated that this publication bias did not impact the estimates (ie, no trimming done because data unchanged). Further sensitivity analysis comparing GLP-1 agonist and basal insulin combination treatment with basal-bolus insulin regimens (three trials;[21,24,25] 1136 participants) showed a mean overall reduction in HbA_{1c} in favour of GLP-1 agonist and basal insulin treatment, with no significant between-study heterogeneity (figure 2).

Pooled analysis of the 14 studies that assessed the proportion of participants achieving an HbA_{1c} of 7·0% or lower at the end of the intervention showed a higher likelihood of achieving this target when participants were treated with GLP-1 agonist and basal insulin combination treatment (absolute risk difference of 17·4%) compared with other treatments, with statistically significant between-study heterogeneity (figure 2). In this analysis, no publication bias was evident (p=0·16; appendix). In the sensitivity analysis comparing the combination treatment with basal-bolus insulin regimens, we saw no treatment benefit with the combination treatment; we detected no significant between-study heterogeneity (figure 2).

Eleven studies (N=3356 participants) assessed the relative risk of any hypoglycaemic events during treatment. Pooling the data of these studies showed no significant difference in the RR of hypoglycaemia with GLP-1 agonist and basal insulin combination treatment compared with other treatments, with statistically significant between-study heterogeneity (figure 3). There was no significant publication bias in this analysis (p=0·81;

appendix). In the sensitivity analysis, GLP-1 agonist and basal insulin combination treatment was associated with a lower risk of hypoglycaemia (absolute risk difference of

See Online for appendix
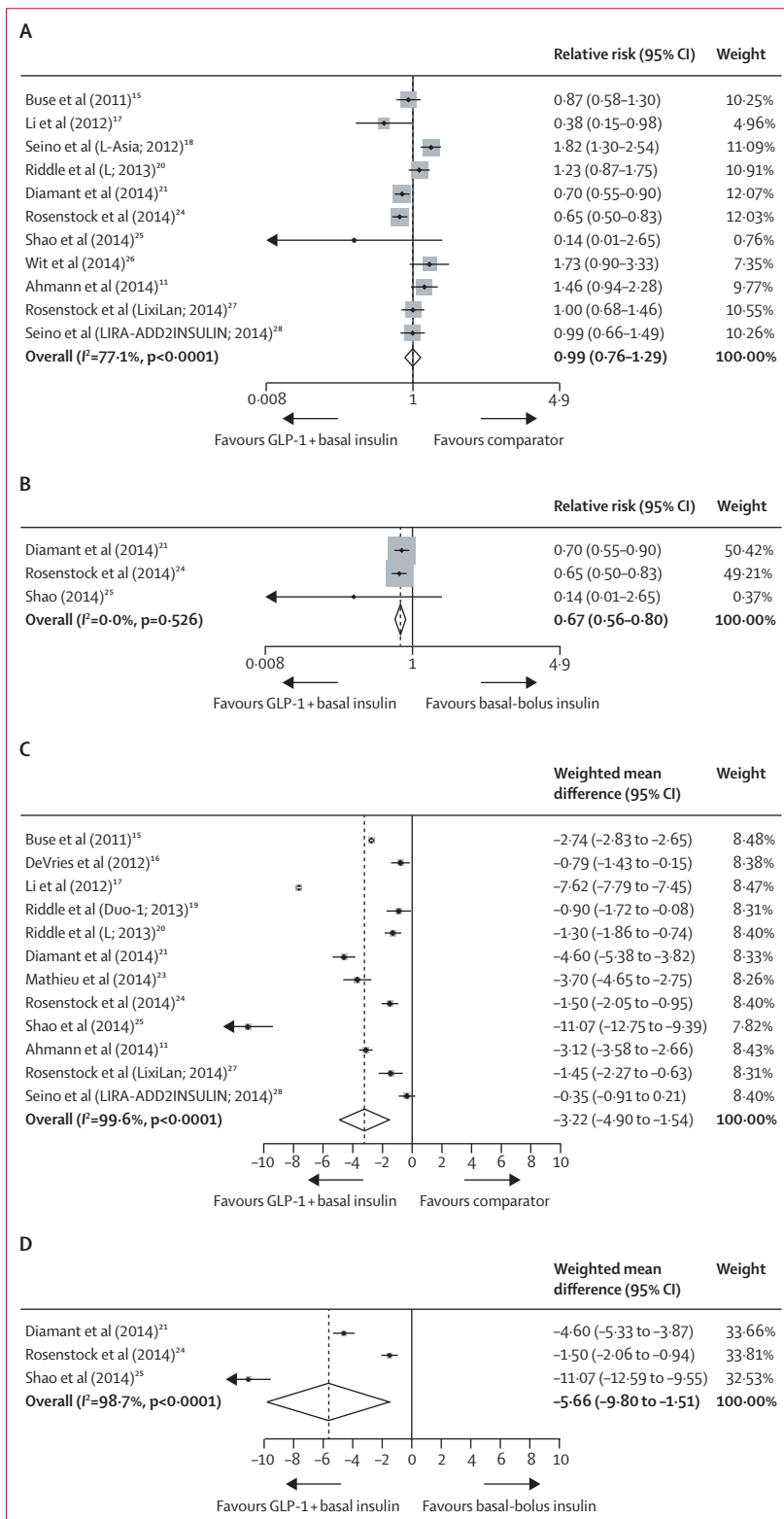
Figure 3: Meta-analyses of glucagon-like peptide-1 (GLP-1) agonist and basal insulin combination treatment versus other anti-diabetic treatments, comparing hypoglycaemia and change in weight
Outcomes assessed are (A) hypoglycaemia, (B) hypoglycaemia in studies that compared combination treatment with basal-bolus insulin treatment, (C) change in weight (kg) at the end of intervention, and (D) change in weight (kg) at the end of intervention in studies that compared combination treatment with basal-bolus insulin treatment. For each estimate, the grey shaded area is the weight of the estimate in proportion to the overall effect.

A

	Relative risk (95% CI)	Weight
Buse et al (2011)[15]	0·87 (0·58–1·30)	10·25%
Li et al (2012)[17]	0·38 (0·15–0·98)	4·96%
Seino et al (L-Asia; 2012)[18]	1·82 (1·30–2·54)	11·09%
Riddle et al (L; 2013)[20]	1·23 (0·87–1·75)	10·91%
Diamant et al (2014)[21]	0·70 (0·55–0·90)	12·07%
Rosenstock et al (2014)[24]	0·65 (0·50–0·83)	12·03%
Shao et al (2014)[25]	0·14 (0·01–2·65)	0·76%
Wit et al (2014)[26]	1·73 (0·90–3·33)	7·35%
Ahmann et al (2014)[11]	1·46 (0·94–2·28)	9·77%
Rosenstock et al (LixiLan; 2014)[27]	1·00 (0·68–1·46)	10·55%
Seino et al (LIRA-ADD2INSULIN; 2014)[28]	0·99 (0·66–1·49)	10·26%
Overall (I^2=77·1%, p<0·0001)	0·99 (0·76–1·29)	100·00%

0·008   1   4·9
Favours GLP-1+basal insulin   Favours comparator

B

	Relative risk (95% CI)	Weight
Diamant et al (2014)[21]	0·70 (0·55–0·90)	50·42%
Rosenstock et al (2014)[24]	0·65 (0·50–0·83)	49·21%
Shao (2014)[25]	0·14 (0·01–2·65)	0·37%
Overall (I^2=0·0%, p=0·526)	0·67 (0·56–0·80)	100·00%

0·008   1   4·9
Favours GLP-1+basal insulin   Favours basal-bolus insulin

C

	Weighted mean difference (95% CI)	Weight
Buse et al (2011)[15]	–2·74 (–2·83 to –2·65)	8·48%
DeVries et al (2012)[16]	–0·79 (–1·43 to –0·15)	8·38%
Li et al (2012)[17]	–7·62 (–7·79 to –7·45)	8·47%
Riddle et al (Duo-1; 2013)[19]	–0·90 (–1·72 to –0·08)	8·31%
Riddle et al (L; 2013)[20]	–1·30 (–1·86 to –0·74)	8·40%
Diamant et al (2014)[21]	–4·60 (–5·38 to –3·82)	8·33%
Mathieu et al (2014)[23]	–3·70 (–4·65 to –2·75)	8·26%
Rosenstock et al (2014)[25]	–1·50 (–2·05 to –0·95)	8·40%
Shao et al (2014)[25]	–11·07 (–12·75 to –9·39)	7·82%
Ahmann et al (2014)[11]	–3·12 (–3·58 to –2·66)	8·43%
Rosenstock et al (LixiLan; 2014)[27]	–1·45 (–2·27 to –0·63)	8·31%
Seino et al (LIRA-ADD2INSULIN; 2014)[28]	–0·35 (–0·91 to 0·21)	8·40%
Overall (I^2=99·6%, p<0·0001)	–3·22 (–4·90 to –1·54)	100·00%

–10 –8 –6 –4 –2 0 2 4 6 8 10
Favours GLP-1+basal insulin   Favours comparator

D

	Weighted mean difference (95% CI)	Weight
Diamant et al (2014)[21]	–4·60 (–5·33 to –3·87)	33·66%
Rosenstock et al (2014)[24]	–1·50 (–2·06 to –0·94)	33·81%
Shao et al (2014)[25]	–11·07 (–12·59 to –9·55)	32·53%
Overall (I^2=98·7%, p<0·0001)	–5·66 (–9·80 to –1·51)	100·00%

–10 –8 –6 –4 –2 0 2 4 6 8 10
Favours GLP-1+basal insulin   Favours basal-bolus insulin

35·1%) than was basal-bolus insulin treatment, with no significant between-study heterogeneity (figure 3).

12 studies (N=3941 participants) assessed participants' change in weight after treatment. Pooling the data of these studies showed that GLP-1 agonist with basal insulin treatment led to a mean reduction in weight that was greater than with other treatment, with statistically significant between-study heterogeneity (figure 3), and we detected no publication bias (p=0·81; appendix). In the sensitivity analysis, combination treatment with GLP-1 agonist and basal insulin led to a mean reduction in weight compared with basal-bolus insulin treatment (figure 3). Although the between-study heterogeneity was statistically significant in this analysis (figure 3), all three trials showed a significant reduction in weight with GLP-1 agonist and basal insulin combination treatment.

Discussion

Our results show that, compared with other anti-diabetic treatments, combination treatment with a GLP-1 agonist and basal insulin can yield improved glycaemic control, with no increase in hypoglycaemia and a reduction in weight. Furthermore, compared with basal-bolus insulin regimens, this combination offers greater HbA_{1c} reduction with lower risk of hypoglycaemia and a reduction in weight. These data thus lend support to GLP-1 agonist and basal insulin combination treatment as a therapeutic strategy that can improve the management of type 2 diabetes.

In the management of type 2 diabetes, the attainment of glycaemic targets is compromised by the limitations of available treatment. With some anti-diabetic treatments (eg, sulfonylureas, insulin), there is an increased risk of hypoglycaemia as glucose concentrations approach the desired normal range. Other drugs (eg, thiazo-lidinediones, insulin) are associated with weight gain, an undesirable effect in patients with diabetes. Third, although they might differ in durability,[29] no anti-diabetic treatment has been shown to prevent the deterioration of β-cell function, which drives the natural history of the disease. Despite its conceptual appeal as a treatment that directly addresses the insulin deficiency inherent in this pathophysiology, even exogenous insulin treatment has practical limitations (hypoglycaemia and weight gain) that undermine its glucose-lowering effectiveness in practice.[4] In this context, the combination of basal insulin with a GLP-1 agonist has been postulated as a novel strategy that can potentially reconcile this management dilemma by facilitating glycaemic regulation while attenuating insulin-associated risks.[8,9]

As shown in figures 2 and 3, our trial has yielded robust and consistent findings that lend support to the benefits of GLP-1 agonist and basal insulin combination treatment. Indeed, this consistency is apparent despite the fact that these studies differ in several ways, including the anti-diabetic treatments assessed, the background oral anti-diabetic drugs, the GLP-1 preparation under study, and the sequence of its initiation in relation to that of basal insulin. Taken together, these studies are supportive of the generalisability across clinical settings of the observed beneficial effects of combining a GLP-1 agonist with basal insulin. Furthermore, it is reassuring that, for both of the glycaemic outcomes and for hypoglycaemia, the between-study heterogeneity that likely reflected the aforementioned differences in study design was eliminated on restriction to only those trials with basal-bolus insulin as the comparator.

Findings from our meta-analysis show an overall beneficial effect on HbA_{1c} of GLP-1 agonist and basal insulin combination treatment versus basal-bolus insulin. This effect was noted despite the fact that the ongoing titration of the bolus insulin could have blunted the overall comparative glucose-lowering benefit of the combination treatment. Moreover, this greater reduction in HbA_{1c} was achieved with a significantly lower risk of hypoglycaemia and pronounced differences in weight. These findings show the comparative beneficial effects of GLP-1 agonists versus bolus insulin, and suggest that GLP-1 agonists should be considered when intensifying treatment in patients on basal insulin. Most importantly, these data are supportive of an important improvement in the management of type 2 diabetes. Specifically, combining a GLP-1 agonist with basal insulin emerges as a treatment strategy that can achieve the ideal triumvirate of short-term outcomes in diabetes management: potent glucose-lowering capacity without increased hypoglycaemia or weight gain.

A limitation of this analysis is that the long-term durability of this treatment is unknown; included trials ranged in duration from 12 weeks to 36 weeks (mean 24·8 weeks). Second, although most of the included studies were published in high-impact journals, there were study features that carry potential risk of bias such as open-label design and pharmaceutical industry funding. Third, there are differences in GLP-1 agonist preparations (which include short-acting, twice-daily formulations, intermediate once-daily versions, and long-acting weekly drugs) that might dictate an optimal choice for combination with basal insulin.[30] For example, short-acting preparations can exert greater reduction of post-prandial glycaemic excursion than longer-acting GLP-1 agonists[31] and hence might be preferable for combination with basal insulin. Combination preparations, in which the relative proportion of GLP-1 agonist to basal insulin is fixed, are in development to enable convenient administration of both drugs with one subcutaneous injection. Additionally, issues such as the long-term durability, safety, and side-effects of GLP-1 agonists have not been established. Finally, the ideal timing for beginning this treatment in the clinical course of the disease is unknown. Although, in general, the trials were done in patients who were late in the course of their diabetes (mean duration 12·2 years) with suboptimal glycaemic control (mean HbA_{1c} 8·13%), GLP-1 agonist, and basal insulin combination treatment yielded a 92% higher likelihood of achieving target HbA_{1c} of 7·0% or lower by the end of the intervention, as compared with

other anti-diabetic treatments. This effectiveness at a point in the natural history of type 2 diabetes when the deterioration of β-cell function is advanced raises the question of whether earlier implementation of this treatment could be particularly beneficial.

Although further studies are needed to establish the optimal approach to the application of this treatment in practice, our findings clearly lend support to the use of GLP-1 agonists in combination with basal insulin in the clinical management of patients with type 2 diabetes.

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