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ORIGINAL ARTICLE

Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis

Sonal Singh MD[1] | Eugene E. Wright Jr. MD[2,3] | Anita Y. M. Kwan MSc[4] |
Juliette C. Thompson BSc[5] | Iqra A. Syed MSc[5] | Ellen E. Korol MSc[5] |
Nathalie A. Waser PhD[5] | Maria B. Yu MSc[6] | Rattan Juneja MD[4]

[1]Johns Hopkins University School of Medicine, Baltimore, Maryland

[2]Department of Medicine, Duke University Medical Center at the Southern Regional Area Health Education Center (AHEC), Fayetteville, North Carolina

[3]Department of Community and Family Medicine, Duke University Medical Center at the Southern Regional Area Health Education Center (AHEC), Fayetteville, North Carolina

[4]Lilly USA, LLC, Indianapolis, Indiana

[5]ICON Epidemiology, Vancouver, British Columbia, Canada

[6]Eli Lilly Canada Inc., Toronto, Ontario, Canada

Corresponding Author: Rattan Juneja MD, Lilly USA, LLC, Lilly Corporate Center, Indianapolis, IN 46285 (rjuneja@lilly.com).

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Aims: Since 2005, several glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been approved to treat people with type 2 diabetes. These agents are considered for use at the same point in the treatment paradigm as basal insulins. A comprehensive comparison of these drug classes, therefore, can help inform treatment decisions. This systematic review and meta-analysis assessed the clinical efficacy and safety of GLP-1 RAs compared with basal insulins.

Materials and methods: MEDLINE, EMBASE, CENTRAL and PubMed databases were searched. Randomized clinical trials (RCTs) of ≥16 weeks' duration comparing GLP-1 RAs vs basal insulins in adults with type 2 diabetes inadequately controlled with oral antihyperglycemic drugs were included. Data on the change from baseline to 26 weeks (±10 weeks) of treatment in hemoglobin A1c (HbA1c) and weight, as well as the proportion of patients experiencing hypoglycaemia, were extracted. Fixed-effect pairwise meta-analyses were conducted where data were available from ≥2 studies.

Results: Fifteen RCTs were identified and 11 were meta-analysed. The once-weekly GLP-1 RAs, exenatide long acting release (LAR) and dulaglutide, led to greater, statistically significant mean HbA1c reductions vs basal insulins (exenatide: −0.31% [95% confidence interval −0.42, −0.19], dulaglutide: −0.39% [−0.49, −0.29]) whilst once-daily liraglutide and twice-daily exenatide did not (liraglutide: 0.06% [−0.06, 0.18], exenatide: 0.01% [−0.11, 0.13]). Mean weight reduction was seen with all GLP-1 RAs while mean weight gain was seen with basal insulins. Interpretation of the analysis of hypoglycaemia was limited by inconsistent definitions and reporting. Because of the limited number of available studies sensitivity analyses to explore heterogeneity could not be conducted.

Conclusions: Although weight reduction is seen with all GLP-1 RA's, only the once-weekly agents, exenatide LAR and dulaglutide, demonstrate significant HbA1c reductions when compared to basal insulins.

KEYWORDS

basal insulin, GLP-1 RAs, glycaemic control, meta-analysis, systematic review, type 2 diabetes

1 | INTRODUCTION

Several drug classes provide options for physicians to improve patients' control of type 2 diabetes. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a novel class of injectable antihyperglycaemic treatments that, when compared to traditional treatment options such as insulin and sulfonylureas (SUs), offer the advantage of regulating insulin secretion in proportion to ambient glucose levels, thus reducing the risk of hypoglycaemia and, at the same time, facilitating weight loss.[1] Various diabetes treatment algorithms include GLP-1 RAs as a therapy option after initial treatment with metformin (MET).[2–4] Since the introduction of exenatide twice daily (BID) for the treatment of type 2 diabetes in 2005, several GLP-1 RAs have been developed and marketed. Increasingly, new GLP-1 RAs are available as once-weekly treatments rather than once- or twice-daily options and in 2014, two new once-weekly GLP-1 RAs received marketing authorization: albiglutide and dulaglutide.[5–8]

The clinical effectiveness and safety of GLP-1 RAs compared to each other and to oral antihyperglycemic drugs (OAD) have been assessed in several meta-analyses.[9–11] However, the positioning of GLP-1 RAs within the treatment paradigm is at the point when the use of basal insulin might also be considered; therefore, there is an increasing desire to understand the similarities and differences between GLP-1 RAs and basal insulins. Although such comparisons have been published,[11–16] they all have limitations to consider. Wang et al.[15] do not include the two new agents (dulaglutide and albiglutide) and, although Karagiannis et al.[10] do include the new treatments, their analysis is limited to only once-weekly GLP-1 RAs. Liu et al.[13] on the other hand, pooled all GLP-1 RAs together when comparing to insulin glargine. Such pooling assumes, a priori, that all GLP-1 RAs are similar in efficacy and pharmacodynamic profile, which is not the case as demonstrated in head-to-head studies.[17,18] More recently, Zaccardi et al.[16] conducted an analysis where GLP-1 RAs were considered independently, but basal insulins were pooled, again making an a priori assumption that all basal insulins have the same efficacy and pharmaocodynamic profile. Pooling also discounts the heterogeneity between GLP-1 RA trials regarding background therapy and drug dosage; as such, it is imperative that heterogeneity using appropriate measures is assessed prior to combining treatments for analytical purposes. To this end, to evaluate the clinical efficacy of GLP-1 RAs, by type, vs basal insulins, we conducted a systematic review of the literature and a series of paired meta-analyses to assess the differences in glycaemic control, weight change and the risk of hypoglycaemia in adults with type 2 diabetes.

2 | MATERIALS AND METHODS

2.1 | Data sources and searches

MEDLINE (including Epub ahead of print and In-process citations), EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from database inception to September 9, 2016. The searches were limited to peer-reviewed studies in the English language. Separate search strategies were designed for each database (MEDLINE strategy is included in Appendix S1, Supporting Information). Each search strategy included free-text, MeSH and EMTREE terms, where appropriate, for type 2 diabetes and GLP-1 RAs, and a randomized controlled trial (RCT) study design filter in MEDLINE and EMBASE.

2.2 | Study selection

Included RCTs were selected based on predefined eligibility criteria using the population, intervention, comparators, outcomes and study design (PICOS) framework. Eligibility criteria included: (1) adults with type 2 diabetes inadequately controlled by OADs; (2) treatment of the majority of subjects with US approved dosages of GLP-1 RA (exenatide 10 μg twice daily, liraglutide 1.2 or 1.8 mg once daily, exenatide 2 mg once weekly (long acting release [LAR]), lixisenatide 20 μg once daily, albiglutide 30 or 50 mg once weekly, and dulaglutide 0.75 or 1.5 mg once weekly plus at least one OAD; (3) comparator arm of basal insulin (ie, insulin detemir, insulin glargine, insulin degludec, neutral protamine hagedorn [NPH] insulin) plus at least one OAD; and (4) RCT duration of at least 16 weeks. Trials performed in treatment-naïve patients with type 2 diabetes, or samples that recruited only patients with comorbidities including renal failure or cardiovascular comorbidities, were excluded. Two reviewers independently determined whether the RCTs met eligibility criteria. Each reviewer first reviewed the titles and abstracts; full-text articles were reviewed where eligibility could not be determined from the title and abstract review alone. Discrepancies between reviewers were resolved by consensus, or adjudicated by a third reviewer.

2.3 | Data extraction and quality assessment

Data extraction was performed by a single experienced data extractor into a customized spreadsheet; key fields were validated by a second extractor. Discrepancies were resolved as described previously for study selection. The extraction form was designed to collect data reporting study design features, baseline patient demographics and clinical characteristics, treatment arm details, efficacy (glycated hemoglobin [HbA1c], weight) and safety outcomes (hypoglycemia, gastrointestinal adverse events).

Endpoints at week 26 ($\pm$10 weeks) were extracted and reported. If data at week 26 were unavailable, the data closest to week 26 between weeks 16 and 36 were included. For trials that presented endpoints in graph format only, values were derived by digitizing the graph, using the WebPlotDigitizer program available online (http://arohatgi.info/WebPlotDigitizer/app/). This was necessary for 4 studies.[19–22] A risk assessment of bias was performed for each included RCT using the Cochrane Collaboration's tool.[23] Two reviewers independently assessed the quality of each included RCT.

2.4 | Data synthesis and statistical analysis

Mean values and associated measures of variability (variance, standard deviation [SD], standard error [SE] or confidence interval [CI]) for continuous endpoints, and counts and proportions for categorical endpoints were extracted. For the purposes of the meta-analyses, if

SD was not reported, it was imputed from other available information (eg, SE or 95% CI), using the prognostic method described by Ma et al.[24] Where sample sizes for HbA1c and weight outcomes were not reported, the intention-to-treat (ITT) population was assumed. Where sample sizes for hypoglycaemia endpoints were not reported, if available, the safety population was assumed; otherwise the ITT population was assumed.

The meta-analyses were conducted using the "meta" statistical package in R version 3.1.3.[25] To understand the difference between GLP-1 RAs and basal insulins by drug, fixed-effect pairwise meta-analyses using the frequentist approach were conducted for the changes in HbA1c and weight, and the occurrence of hypoglycaemia outcomes. Random effects analysis were considered where appreciable statistical heterogeneity was observed. However, when a small number of studies are available for analysis, as was the case for this analysis, random effects analysis shows poor precision of between-study variance, and are therefore not appropriate.[26] In keeping with the Cochrane handbook, meta-analyses were conducted where data were available for at least 2 separate trials with the same treatments.[27] If data for a treatment were identified in only 1 trial, meta-analysis was not conducted; however, the trial results are shown. "Hypoglycaemia" outcomes included all attributions of hypoglycaemia in a publication (irrespective of blood glucose value), including severe hypoglycaemia. The "severe hypoglycaemia" category included publication attribution as severe or major hypoglycaemia or definition of "requiring third-party assistance." However, meta-analysis for severe hypoglycaemia could not be conducted because of low event rates; as such, only the proportion of patients experiencing severe hypoglycaemia events in GLP-1 RA groups vs basal insulins were extracted and presented. To calculate the weight contribution by individual trials to the overall effect estimate, the inverse variance method for continuous outcomes and the Mantel-Haenszel for categorical outcomes were used.

Statistical tests of heterogeneity were conducted to understand the extent to which the results of trials included in the meta-analysis were consistent. The main measure of heterogeneity used for evaluation was I^2 value.[27] Sub-group sensitivity analysis was conducted by excluding one study to understand the impact of non-standard dosing used in a minority (37.9%) of patients.[20]

Each model was coded, analysed and summarized using forest plots. The forest plots summarize effect estimates from all included trials to provide a comprehensive view of available evidence, as well as a pooled effect size from meta-analysis. For change in HbA1c and weight, a mean difference <0 signifies the result favouring the GLP-1 RA arm compared to the basal insulin arm, ie, a greater reduction in HbA1c or weight compared to basal insulin. For hypoglycaemia, an odds ratio <1 indicates lower odds in the GLP-1 RA arm compared to basal insulin. Where meta-analyses were conducted (ie, 2 or more trials were available for a treatment and comparator), I^2 value was also reported. Codes designed for meta-analyses and their outputs were validated by a second analyst.

3 | RESULTS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram documenting the RCT selection process is provided in Figure 1. A total of 2694 articles were identified, of which 19 articles describing 15 RCTs were eligible for inclusion in the systematic literature review. Key study and baseline characteristics, including background therapy, are presented in Table 1. The eligible RCTs included comparisons of exenatide 10 μg

IDENTIFICATION

Database inception - October 2015
2,255 records identified by database searching:
- MEDLINE (inc. In-process) (n=792)
- EMBASE (n=887)
- Cochrane (n=567)
- PubMed (Epub ahead of print) (n=9)

01 January 2015 – September 2016
776 records identified by database searching:
- MEDLINE (inc. Epub ahead of print and In-process) (n=314)
- EMBASE (n=250)
- Cochrane (n=212)

1,378 records after duplicates removed

439 records after duplicates removed

SCREENING

1,817 records screened for eligibility

1,755 records excluded

ELIGIBILITY

62 full-text articles assessed for eligibility

43 full-text articles excluded due to:
Inappropriate study design (n=27)
Inappropriate intervention (n=6)
Inappropriate outcome (n=4)
Not English language (n=2)
Duplicates (n=4)

INCLUDED

19 articles included in systematic literature review (describing 15 RCTs)
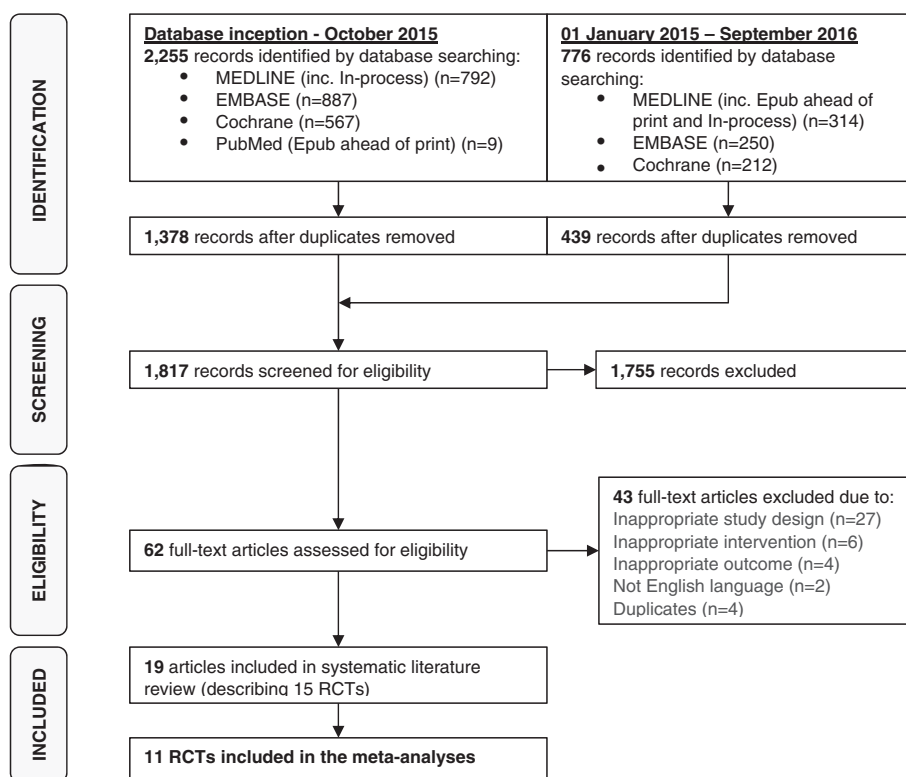
11 RCTs included in the meta-analyses

FIGURE 1 Study PRISMA diagram. Abbreviations: RCT, randomized clinical trial.

TABLE 1 Study population baseline characteristics, background therapies, and presence of key three endpoints

Trial name and author	Study duration (weeks)	Intervention	Mean age (SD), years	Female, %	White, %	Mean disease duration (SD), years	Mean HbA1c (SD), %	Mean HbA1c (mmol/mol)	Mean bodyweight (SD), kg	Mean BMI (SD), kg/m^2	Background therapy, %
Exenatide 10 μg twice daily vs insulin glargine											
Bunck 2009	52	Exenatide[1]	58.4 (–)	36.1	–	5.7 (–)	7.6 (–)	60	90.6 (–)	30.9 (–)	MET (100%)
		Glargine	58.3 (–)	33.3	–	4.0 (–)	7.4 (–)	57	92.4 (–)	30.1 (–)	
HEELA (Davies 2009)	26	Exenatide	56.8 (10.2)	29.7	–	9.0 (4.6)	8.7 (0.7)	72	101.4 (19.8)	34.6 (5.7)	Double/triple therapy MET ± SU ± TZD
		Glargine	56.2 (7.9)	33.6	–	8.4 (4.4)	8.5 (0.7)	69	97.6 (16.4)	33.7 (4.9)	
Heine 2005	26	Exenatide	59.8 (8.8)	45.0	80	9.9 (6.0)	8.2 (1.0)	66	87.5 (16.9)	31.4 (4.4)	MET + SU (100%)
		Glargine	58.0 (9.5)	43.4	81	9.2 (5.7)	8.3 (1.0)	67	88.3 (17.9)	31.3 (4.6)	
Gurkan 2014	26	Exenatide	52.2 (7.3)	70.0	–	6.9 (3.3)	8.0 (0.8)	64	94.3 (11.8)	35.9 (3.7)	MET (100%)
		Glargine	53.1 (7.0)	58.8	–	7.6 (4.3)	8.1 (0.8)	65	90.5 (14.3)	33.2 (4.5)	
Barnett 2007	32	Exenatide	54.5 (–)	51.5	–	6.6 (–)	8.9 (–)	74	85.6 (–)	31.3 (–)	MET (55%-56%) or SU (44%-46%)
		Glargine	55.3 (–)	54.3	–	8.3 (–)	9.0 (–)	75	84.0 (–)	30.9 (–)	
Exenatide 2 mg once weekly vs insulin glargine											
DURATION-3 (Diamant 2010, 2014)	156	Exenatide	58.0 (10.0)	48.0	82	8.0 (6.0)	8.3 (1.1)	67	91.2 (18.6)	32.3 (5.4)	MET (70%)
		Glargine	58.0 (9.0)	45.0	85	7.8 (6.0)	8.3 (1.0)	67	90.6 (16.4)	32.3 (4.8)	
Inagaki 2012	62	Exenatide	57.1 (10.4)	34.0	0[2]	8.9 (6.1)	8.5 (0.8)	69	70.0 (13.3)	26.1 (4.03)	MET (67%), BG + TZD (33%)
		Glargine	56.4 (11.2)	30.2	0[2]	9.2 (6.0)	8.5 (0.8)	69	71.0 (13.9)	26.2 (3.8)	
Exenatide 2 mg once weekly vs insulin detemir											
Davies 2013	30	Exenatide	59.0 (10.0)	36.0	94	8.0 (6.0)	8.4 (0.9)	68	96.7 (17.0)	33.7 (4.7)	MET (100%) + SU (70%-72%)
		Detemir	58.0 (10.0)	31.0	97	7.0 (5.0)	8.4 (0.9)	68	97.9 (15.8)	33.7 (4.7)	
Liraglutide 1.8 mg once daily vs insulin glargine											
EAGLE (D'Alessio 2015)	24	Liraglutide	57.4 (8.9)	44.0	–	–	9.1 (1.1)	76	90.1 (16.7)	31.8 (4.1)	MET + SU[3]
		Glargine	57.1 (8.8)	47.3	–	–	9.0 (1.0)	75	90.8 (16.6)	32.0 (4.2)	
LEAD-5 (Russell-Jones 2009)	26	Liraglutide	57.6 (9.5)	43.0	–	9.2 (5.8)	8.3 (0.9)	67	85.5 (19.4)	30.4 (5.3)	MET + SU (94%-95%)
		Glargine	57.5 (10.5)	40.0	–	9.7 (6.4)	8.2 (0.9)	66	85.0 (17.9)	30.3 (5.3)	
Liraglutide 1.8 mg once daily vs insulin degludec											
DUAL-I (Gough 2014, 2015)	52	Liraglutide	55.0 (10.2)	50.0	62	7.2 (6.1)	8.3 (0.9)	67	87.4 (18.0)	31.3 (4.8)	MET (82%-83%), MET + TZD (17%-18%)
		Degludec	54.9 (9.7)	52.0	62	7.0 (5.3)	8.3 (1.0)	67	87.4 (19.2)	31.2 (5.3)	
Albiglutide 30 mg once weekly vs insulin glargine											
HARMONY4 (Weissman 2014)	156	Albiglutide	55.8 (9.3)	43.3	69	8.9 (6.5)	8.3 (0.9)	67	95.1 (19.7)	33.2 (5.6)	MET + SU (82%)
		Glargine	54.7 (9.8)	45.2	66	8.4 (5.7)	8.4 (1.0)	68	94.6 (19.1)	33.0 (5.4)	

TABLE 1 Continued

Dulaglutide once weekly vs insulin glargine

Trial name and author	Study duration (weeks)	Intervention	Mean age (SD), years	Female, %	White, %	Mean disease duration (SD), years	Mean HbA1c (SD), %	Mean HbA1c (mmol/mol)	Mean bodyweight (SD), kg	Mean BMI (SD), kg/m²	Background therapy, %
AWARD-2 (Giorgino 2015)	78	Dulaglutide 0.75 mg	57.0 (9.0)	50.0	71	9.0 (6.0)	8.1 (1.0)	65	86.0 (18.0)	32.0 (5.0)	MET + SU (65%-68%)
		Dulaglutide 1.5 mg	56.0 (10.0)	47.0	71	9.0 (6.0)	8.2 (1.0)	66	85.0 (18.0)	31.0 (5.0)	
		Glargine	57.0 (9.0)	49.0	70	9.0 (6.0)	8.1 (1.0)	65	88.0 (20.0)	32.0 (6.0)	
Araki 2015	34	Dulaglutide 0.75 mg	57.5 (10.5)	31.0	0[2]	8.9 (6.7)	8.1 (0.8)	65	70.9 (13.7)	26.1 (3.6)	MET ± SU[4]
	30	Glargine	56.1 (11.3)	26.0	0[2]	8.8 (6.1)	8.0 (0.9)	64	71.1 (13.8)	25.9 (3.9)	

Lixisenatide versus insulin glargine

Trial name and author	Study duration (weeks)	Intervention	Mean age (SD), years	Female, %	White, %	Mean disease duration (SD), years	Mean HbA1c (SD), %	Mean HbA1c (mmol/mol)	Mean bodyweight (SD), kg	Mean BMI (SD), kg/m²	Background therapy, %
LixiLan-O (Rosenstock 2016)		Lixisenatide 20 µg	58.7 (8.7)	43.2	92.3	8.9 (6.3)	8.1 (0.7)	65	90.8 (16.3)	32.0 (4.4)	MET
	30	Glargine	58.3 (9.4)	49.3	90.1	8.7 (5.6)	8.1 (0.7)	65	89.8 (16.3)	31.7 (4.5)	

Abbreviations: BG, biguanine; BMI, body mass index; HbA1c, glycated hemoglobin; MET, metformin; SD, standard deviation; SU, sulfonylurea; TZD, thiazolidinedione.

1 The majority of participants received exenatide 10 µg twice daily.

2 Trial conducted in a Japanese population.

3 Insulin glargine arm: MET = 99.6%, SU = 67.5%, SUs taken by 60% of participants at baseline and reduced to 49% at 24 weeks, liraglutide arm: MET = 99.8%, SU = 68.3%, SUs taken by 63% of participants at baseline and reduced to 48% at 24 weeks. SUs were reduced or discontinued at investigators discretion.

4 Dulaglutide arm: SU monotherapy (19%), MET monotherapy (35%), SU + MET (46%). Insulin glargine arm: SU monotherapy (18%), MET monotherapy (37%), SU + MET (45%).

or 2 mg, liraglutide 1.8 mg, albiglutide 30 mg (uptitrated to 50 mg as needed), dulaglutide 0.75 or 1.5 mg or lixisenatide 20 μg with insulin detemir, glargine or degludec. Eligible studies reporting NPH insulin were not identified. Study endpoints were reported at 16, 24, 26, 28, 52, 78, 156 and 168 weeks. Fifteen RCTs reported HbA1c and body-weight change from baseline, 9 reported hypoglycemic episodes and 11 reported severe hypoglycemic episodes. As data for the dulaglutide 1.5 mg dose, albiglutide 30 and 50 mg doses and lixisentatide 20 μg were identified in only 1 study each, meta-analysis could not be performed for these doses. The insulin titration algorithms and fasting plasma glucose (FPG) targets are shown in Table S1, Supporting Information. HbA1c, weight and FPG change from baseline are shown in Tables S2 to S4, Supporting Information respectively.

Mean patient age in the included studies ranged from 52.2 to 59.8 years and mean disease duration ranged from 4.0 to 9.9 years. Slightly more males were represented in the study populations. Mean baseline HbA1c levels ranged from 7.4% to 9.1% (57-76 mmol/mol); the median across trials was 8.2%. Mean bodyweight ranged from 69.95 to 101.40 kg and mean body mass index (BMI) ranged from 25.90 to 35.89 kg/m^{2}. Mean fasting glucose values at baseline varied from 8.6 to 12.2 mmol/L (Table S4, Supporting Information). Two trials were conducted in Asian populations[28,29] and the other trials that reported ethnicity were conducted in mostly white populations.[21,22,30–35]

3.1 | Risk of bias

The risk of bias for all trials included is presented in Figure S1, Supporting Information. Selection bias was assessed as unclear in 7 trials[20,22,31,36–39] for random sequence generation and in 4 trials[20,36–38] for allocation concealment. Absence of reporting was the main reason for the decision to assign an RCT as presenting unclear risk of bias. All trials were open label. Attrition bias (see incomplete outcome data) was assessed to be low in 12 trials[19–22,28–31,33–35,38] (percentage of patients lost to follow-up reported as 0%-3% in all arms) and was unclear in 3.[36,37,39] Two trials were deemed to have an unclear risk with regard to reporting.[36,37]

3.2 | Efficacy outcomes

3.2.1 | Glycemic control

Of the 15 RCTs identified by the systematic review, 11 studies reported change in HbA1c at 26 weeks (±10 weeks) and had comparable data from at least 2 studies to allow for a pairwise meta-analysis. These included 5 trials of exenatide 10 μg vs insulin glargine[19,20,34,37,38]; 2 trials of exenatide 2 mg LAR vs insulin glargine[29,33]; 2 trials of liraglutide 1.8 mg vs insulin glargine[36,39]; and 2 trials of dulaglutide 0.75 mg vs insulin glargine.[21,28] Four studies could not be included in the pair-wise meta-analysis as the requirement of comparable data for the same dose or comparator insulin from 2 studies was not met. These studies compared exenatide 2 mg LAR vs insulin detemir,[30] liraglutide 1.8 mg vs insulin degludec,[31] albiglutide 30 mg titrated to 50 mg (as required) vs insulin glargine[22] and lixisentatide 20 μg vs insulin glargine.[35] In addition, although 2 studies were available for a pair-wise meta-analysis of the 0.75 mg dose of dulaglutide[21,28] to be performed, only 1 study reported both doses of

dulaglutide (0.75 and 1.5 mg).[21] In the absence of another study with the 1.5 mg dose, a pair-wise analysis for this dose could not be performed. A summary of all evidence identified by the systematic review and the results of the pairwise meta-analyses are presented in Figure 2A. Mean HbA1c changes from baseline as well as the percentage of patients achieving HbA1c < 7% (53 mmol/L) are presented in Table S2, Supporting Information.

Compared with insulin glargine, the mean difference in HbA1c change was +0.01% (95% CI, −0.11, 0.13; I[2] = 0%) (+0.01 mmol/L [95% CI, −1.2, 1.4]) with exenatide 10 μg, −0.31% (95% CI, −0.42, −0.19; I[2] = 75%) (−3.4 mmol/L [95% CI, −4.6, −2.1]) with exenatide 2 mg LAR, +0.06%, (95% CI, −0.06, 0.18; I[2] = 86.1%) (+0.7 mmol/L [95% CI, −0.7, 2.0]) with liraglutide 1.8 mg and −0.39% (95% CI, −0.49, −0.29; I[2] = 88.6%) (−0.43 mmol/L [95% CI, −5.4, −3.2]) with dulaglutide 0.75 mg (Figure 2A).

The RCT conducted by Bunck et al.20 included 5 different doses of exenatide: 10 μg BID (62.1% of participants), 15 μg BID (3.4%), 10 μg 3 times daily (TID) (6.9%), 15 μg TID (3.4%) and 20 μg TID (17.2%). This RCT was included in the systematic literature review because the majority of participants (62.1%) received a licensed dose of exenatide (10 μg BID). However, because of the different doses of exenatide administered to patients as compared to other exenatide 10 μg BID trials, sensitivity analyses for HbA1c and weight were conducted to understand the impact of this trial on the overall pooled estimate and heterogeneity. This sensitivity analysis showed no impact on the overall effect estimate or heterogeneity measure for exenatide 10 μg BID vs insulin glargine with a pooled mean HbA1c change of +0.01% (95% CI, −0.11, 0.13; I[2] = 0%), (+3.2 mmol/L [95% CI, −1.2, 1.4]), which is the same as the pooled estimates when including the Bunck et al. trial.

3.2.2 | Body weight

A summary of all evidence for bodyweight, as well as the pairwise meta-analyses at 26 weeks, are presented in Figure 2B. Compared with insulin glargine, the mean difference in bodyweight was −4.31 kg (95% CI, −4.71, −3.90; I[2] = 76%) with exenatide 10 μg, −2.85 kg (95% CI, −3.20, −2.49; I[2] = 96.5%) with exenatide 2 mg LAR, −4.65 kg (95% CI, −5.08, −4.22; I[2] = 89.1%) with liraglutide 1.8 mg, and −1.98 kg (95% CI, −2.32, −1.64, I[2] = 91%) with dulaglutide 0.75 mg. Removing the RCT conducted by Bunck et al.[20] minimally changed the overall effect estimate for exenatide 10 μg to −4.35 kg (95% CI, −4.77, −3.93; I[2] = 81.5%). Mean bodyweight and BMI change from baseline are presented in Table S3, Supporting Information.

3.3 | Safety outcomes

3.3.1 | Hypoglycaemia

A summary of all evidence for hypoglycaemia as well as the pairwise meta-analyses at 26 weeks are presented in Figure 3A. Compared to insulin glargine, the odds ratio for a hypoglycaemic episode was 0.32 (95% CI, 0.22, 0.47; I[2] = 33.2%) with exenatide 2 mg LAR and 0.40 (95% CI, 0.32, 0.51; I[2] = 96%) with liraglutide 1.8 mg. A summary of the evidence related to the proportion of patients experiencing a hypoglycaemic episode and the background therapy is presented in Figure 3B.
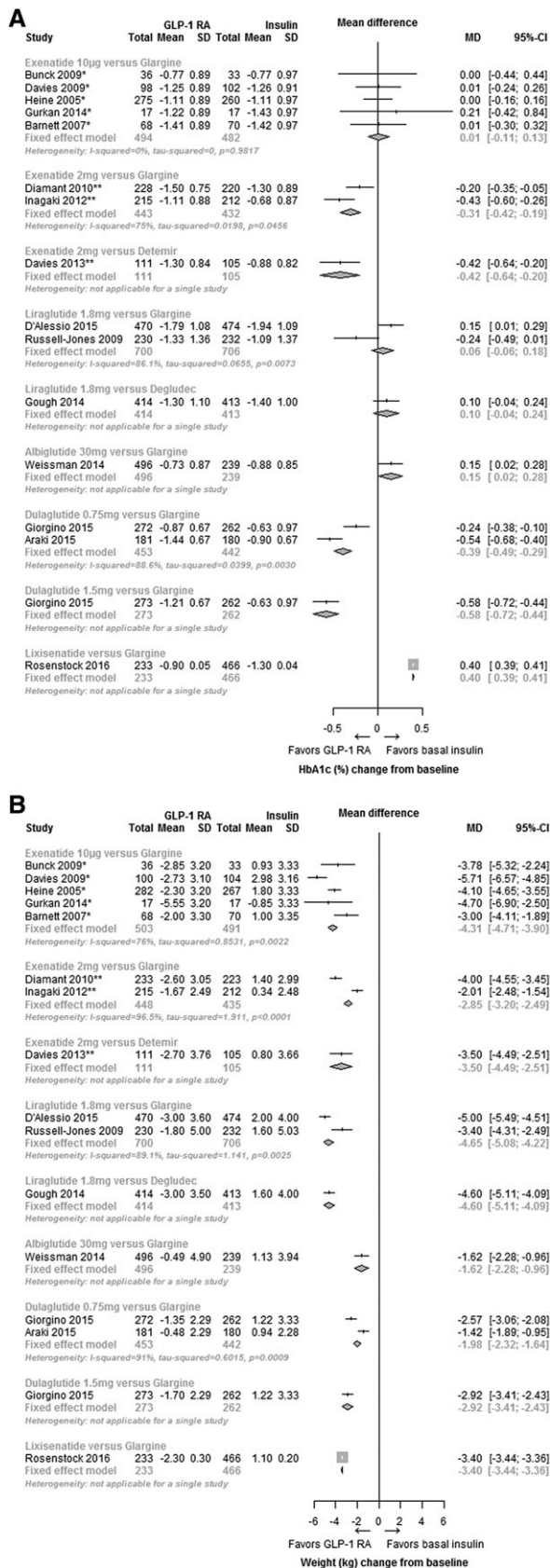
A

Study	GLP-1 RA Total	Mean	SD	Insulin Total	Mean	SD	Mean difference	MD	95%-CI
Exenatide 10µg versus Glargine									
Bunck 2009*	36	-0.77	0.89	33	-0.77	0.97		0.00	[-0.44; 0.44]
Davies 2009*	98	-1.25	0.89	102	-1.26	0.91		0.01	[-0.24; 0.26]
Heine 2005*	275	-1.11	0.89	260	-1.11	0.97		0.00	[-0.16; 0.16]
Gurkan 2014*	17	-1.22	0.89	17	-1.43	0.97		0.21	[-0.42; 0.84]
Barnett 2007*	68	-1.41	0.89	70	-1.42	0.97		0.01	[-0.30; 0.32]
Fixed effect model	494			482				0.01	[-0.11; 0.13]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.9817									
Exenatide 2mg versus Glargine									
Diamant 2010**	228	-1.50	0.75	220	-1.30	0.89		-0.20	[-0.35; -0.05]
Inagaki 2012**	215	-1.11	0.88	212	-0.68	0.87		-0.43	[-0.60; -0.26]
Fixed effect model	443			432				-0.31	[-0.42; -0.19]
Heterogeneity: I-squared=75%, tau-squared=0.0198, p=0.0456									
Exenatide 2mg versus Detemir									
Davies 2013**	111	-1.30	0.84	105	-0.88	0.82		-0.42	[-0.64; -0.20]
Fixed effect model	111			105				-0.42	[-0.64; -0.20]
Heterogeneity: not applicable for a single study									
Liraglutide 1.8mg versus Glargine									
D'Alessio 2015	470	-1.79	1.08	474	-1.94	1.09		0.15	[0.01; 0.29]
Russell-Jones 2009	230	-1.33	1.36	232	-1.09	1.37		-0.24	[-0.49; 0.01]
Fixed effect model	700			706				0.06	[-0.06; 0.18]
Heterogeneity: I-squared=86.1%, tau-squared=0.0655, p=0.0073									
Liraglutide 1.8mg versus Degludec									
Gough 2014	414	-1.30	1.10	413	-1.40	1.00		0.10	[-0.04; 0.24]
Fixed effect model	414			413				0.10	[-0.04; 0.24]
Heterogeneity: not applicable for a single study									
Albiglutide 30mg versus Glargine									
Weissman 2014	496	-0.73	0.87	239	-0.88	0.85		0.15	[0.02; 0.28]
Fixed effect model	496			239				0.15	[0.02; 0.28]
Heterogeneity: not applicable for a single study									
Dulaglutide 0.75mg versus Glargine									
Giorgino 2015	272	-0.87	0.67	262	-0.63	0.97		-0.24	[-0.38; -0.10]
Araki 2015	181	-1.44	0.67	180	-0.90	0.67		-0.54	[-0.68; -0.40]
Fixed effect model	453			442				-0.39	[-0.49; -0.29]
Heterogeneity: I-squared=88.6%, tau-squared=0.0399, p=0.0030									
Dulaglutide 1.5mg versus Glargine									
Giorgino 2015	273	-1.21	0.67	262	-0.63	0.97		-0.58	[-0.72; -0.44]
Fixed effect model	273			262				-0.58	[-0.72; -0.44]
Heterogeneity: not applicable for a single study									
Lixisenatide versus Glargine									
Rosenstock 2016	233	-0.90	0.05	466	-1.30	0.04		0.40	[0.39; 0.41]
Fixed effect model	233			466				0.40	[0.39; 0.41]
Heterogeneity: not applicable for a single study									

-0.5 0 0.5
← Favors GLP-1 RA   Favors basal insulin →
HbA1c (%) change from baseline

B

Study	GLP-1 RA Total	Mean	SD	Insulin Total	Mean	SD	Mean difference	MD	95%-CI
Exenatide 10µg versus Glargine									
Bunck 2009*	36	-2.85	3.20	33	0.93	3.33		-3.78	[-5.32; -2.24]
Davies 2009*	100	-2.73	3.10	104	2.98	3.16		-5.71	[-6.57; -4.85]
Heine 2005*	282	-2.30	3.20	267	1.80	3.33		-4.10	[-4.65; -3.55]
Gurkan 2014*	17	-5.55	3.20	17	-0.85	3.33		-4.70	[-6.90; -2.50]
Barnett 2007*	68	-2.00	3.30	70	1.00	3.35		-3.00	[-4.11; -1.89]
Fixed effect model	503			491				-4.31	[-4.71; -3.90]
Heterogeneity: I-squared=76%, tau-squared=0.8531, p=0.0022									
Exenatide 2mg versus Glargine									
Diamant 2010**	233	-2.60	3.05	223	1.40	2.99		-4.00	[-4.55; -3.45]
Inagaki 2012**	215	-1.67	2.49	212	0.34	2.48		-2.01	[-2.48; -1.54]
Fixed effect model	448			435				-2.85	[-3.20; -2.49]
Heterogeneity: I-squared=96.5%, tau-squared=1.911, p<0.0001									
Exenatide 2mg versus Detemir									
Davies 2013**	111	-2.70	3.76	105	0.80	3.66		-3.50	[-4.49; -2.51]
Fixed effect model	111			105				-3.50	[-4.49; -2.51]
Heterogeneity: not applicable for a single study									
Liraglutide 1.8mg versus Glargine									
D'Alessio 2015	470	-3.00	3.60	474	2.00	4.00		-5.00	[-5.49; -4.51]
Russell-Jones 2009	230	-1.80	5.00	232	1.60	5.03		-3.40	[-4.31; -2.49]
Fixed effect model	700			706				-4.65	[-5.08; -4.22]
Heterogeneity: I-squared=89.1%, tau-squared=1.141, p=0.0025									
Liraglutide 1.8mg versus Degludec									
Gough 2014	414	-3.00	3.50	413	1.60	4.00		-4.60	[-5.11; -4.09]
Fixed effect model	414			413				-4.60	[-5.11; -4.09]
Heterogeneity: not applicable for a single study									
Albiglutide 30mg versus Glargine									
Weissman 2014	496	-0.49	4.90	239	1.13	3.94		-1.62	[-2.28; -0.96]
Fixed effect model	496			239				-1.62	[-2.28; -0.96]
Heterogeneity: not applicable for a single study									
Dulaglutide 0.75mg versus Glargine									
Giorgino 2015	272	-1.35	2.29	262	1.22	3.33		-2.57	[-3.06; -2.08]
Araki 2015	181	-0.48	2.29	180	0.94	2.28		-1.42	[-1.89; -0.95]
Fixed effect model	453			442				-1.98	[-2.32; -1.64]
Heterogeneity: I-squared=91%, tau-squared=0.6015, p=0.0009									
Dulaglutide 1.5mg versus Glargine									
Giorgino 2015	273	-1.70	2.29	262	1.22	3.33		-2.92	[-3.41; -2.43]
Fixed effect model	273			262				-2.92	[-3.41; -2.43]
Heterogeneity: not applicable for a single study									
Lixisenatide versus Glargine									
Rosenstock 2016	233	-2.30	0.30	466	1.10	0.20		-3.40	[-3.44; -3.36]
Fixed effect model	233			466				-3.40	[-3.44; -3.36]
Heterogeneity: not applicable for a single study									

-6 -4 -2 0 2 4 6
← Favors GLP-1 RA   Favors basal insulin →
Weight (kg) change from baseline

FIGURE 2 Effect of GLP-1 RA compared to basal insulin at week 26 (±10 weeks). Change in HbA1c (%) (A), and change in bodyweight (kg) (B). Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MD, mean difference; SD, standard deviation. *Twice daily; **once weekly.

Out of the 15 studies that reported data at week 26 (±10 weeks), 11 RCTs reported data for severe hypoglycaemia. Meta-analyses of severe hypoglycaemia were not conducted because of the limited events observed; 3 studies reported no events in both arms[28–30] and 5 studies reported no events in one arm.[19,31,35,36,39] The numbers and proportions of patients experiencing an episode of hypoglycaemia or an episode of severe hypoglycaemia, and the definitions of hypoglycaemia and severe hypoglycaemia as described by the authors are presented in Table S5, Supporting Information.

### 3.3.2 | Gastrointestinal events

Meta-analyses of gastrointestinal events were not conducted as reporting across studies was insufficient to allow meaningful analyses (data not shown).

4 | DISCUSSION

The meta-analyses show statistically significant reductions in HbA1c with once-weekly exenatide 2 mg LAR and once-weekly dulaglutide 0.75 mg, compared to insulin glargine at 6 months, a reduction in HbA1c of 0.3% (3.3 mmol/L) and 0.4% (4.4 mmol/L), respectively. In contrast, once-daily liraglutide and twice-daily exenatide 10 µg did not show a statistically significant difference from insulin glargine. This difference between weekly and daily GLP-1 RAs may be attributed to the potential impact of the weekly agents on both FPG and postprandial plasma glucose (PPG), compared to the daily agents that may predominantly regulate PPG.

The systematic review identified 15 trials reporting results at 26 weeks (±10 weeks). Eleven trials were included in pair-wise meta-analyses: 5 trials of exenatide 10 µg vs insulin glargine[19,20,34,37,38]; 2 trials of exenatide 2 mg LAR vs insulin glargine[29,33]; 2 trials of liraglutide 1.8 mg vs insulin glargine[36,39]; and 2 trials of dulaglutide 0.75 mg vs insulin glargine.[21,28] Although it was not possible to incorporate data for dulaglutide 1.5 mg, lixisenatide or albiglutide into the analyses, as only 1 study for each met the inclusion criteria and at least 2 studies are required for meta-analysis, it should be considered that the 3-armed trial identified by the systematic review that included the 1.5 mg dulaglutide dose (vs dulaglutide 0.75 mg and insulin glargine) indicated that the higher dose led to a greater reduction in HbA1c and bodyweight compared to both dulaglutide 0.75 mg and insulin glargine (Figure 2).[21] With lixisenatide, a weight reduction was observed compared to insulin glarine, but HbA1c reduction was greater with glargine (Figure 2).[35] With albiglutide, although there was weight reduction when compared with insulin glargine, HbA1c reduction was not different from insulin glargine (Figure 2).[22] This finding is not unexpected, however, as albiglutide was inferior in glycaemic lowering efficacy when compared to liraglutide, which in this meta-analysis also did not have a statistically significant HbA1c reduction when compared to insulin glargine.[18] Analyses conducted for weight change from baseline demonstrated statistically significant weight loss with all GLP-1 RAs compared to weight gain with basal insulins: −4.65 kg (95% CI −5.08, −4.22) for liraglutide 1.8 mg, −4.31 kg (95% CI −4.71, −3.90) for exenatide 10 µg,

FIGURE 3 Effect of GLP-1 RA compared to basal insulin at 26 weeks (±10 weeks) on hypoglycemia, odds ratio (A), and proportion (%) (B). Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OR, odds ratio; prop, proportion. *Twice daily; **once weekly. †At baseline, the majority of patients in each treatment group (exenatide 84.7%; insulin glargine 86.2%) were taking SUs. ††At baseline, 70.0% and 30.0% of patients in both arms were receiving MET and MET + SU, respectively. One in four patients had a reduction in SU dose. ‡SU dosage was reduced or discontinued at the physician's discretion. SUs were initially taken by 60.0% of those receiving insulin glargine and by 63.0% receiving liraglutide. At 24 weeks, 49.0% and 48.0%, respectively, were still taking them. ‡‡At baseline, 94.0% in the liraglutide arm and 95.0% in the insulin glargine arm were receiving SU. ‡‡‡The majority of the patients in the dulaglutide group (65.0%) and insulin glargine group (63.0%) received SU at baseline. In the dulaglutide and insulin glargine groups, 13/117 (11.1%) and 11/114 (9.6%) patients, respectively, decreased their concomitant SU dose from baseline as a result of hypoglycemia. §Figure includes only insulin glargine trials to highlight the differences in proportions of patients experiencing hypoglycemic events between trials, which may be due to variations in insulin titration and background therapies.
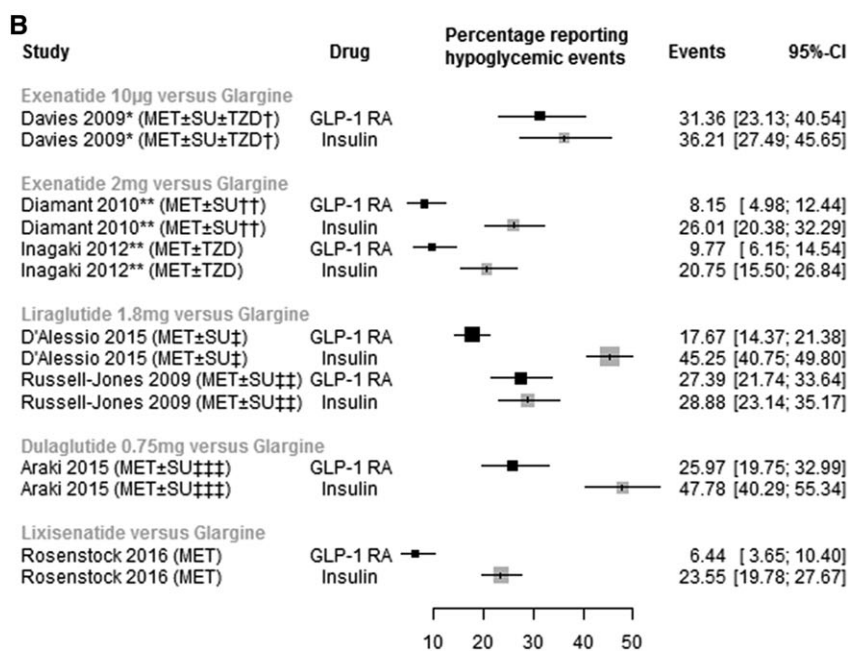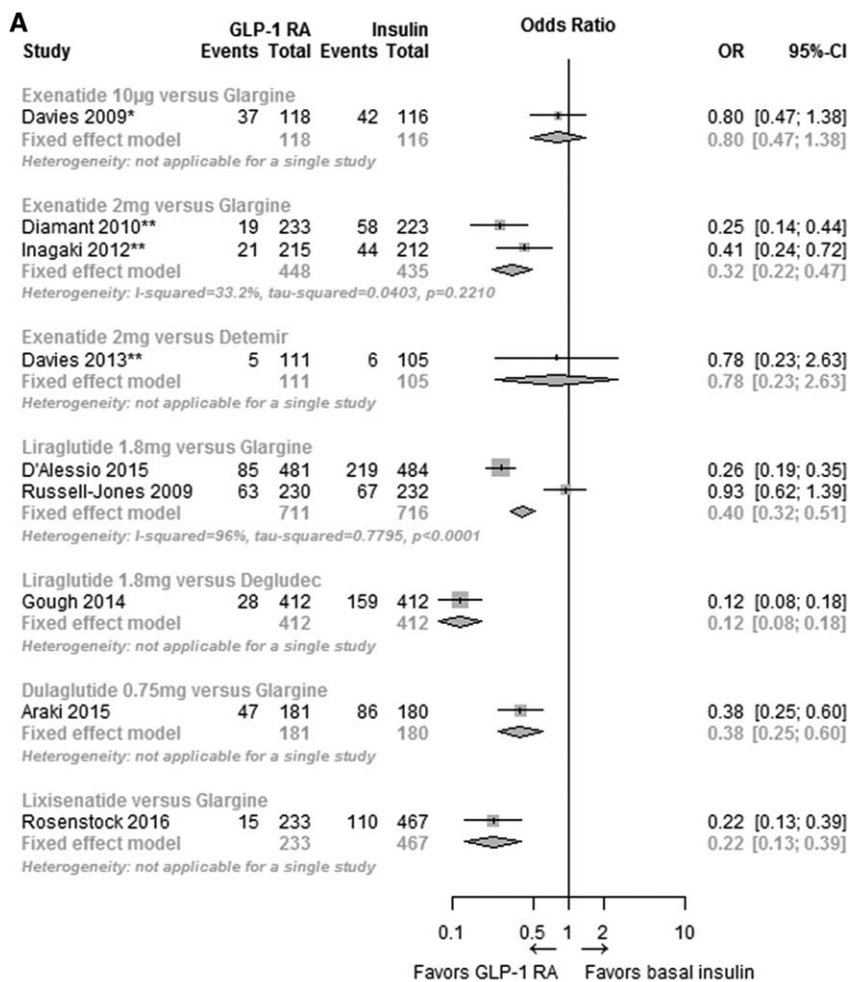
−2.85 kg (95% CI −3.20 to −2.49) for exenatide 2 mg LAR, and −1.98 kg (95% CI −2.32, −1.64) for dulaglutide 0.75 mg.

The results of the 2 pairwise meta-analyses indicated that there is a lower risk of hypoglycaemia with liraglutide 1.8 mg once daily compared to insulin glargine and also with once-weekly exenatide 2 mg LAR compared to insulin glargine. However, these results should be interpreted with caution because of the variability in definitions of hypoglycaemia in different studies, a challenge that has been identified by the American Diabetes Association.[40] Moreover, there were only limited data available for severe hypoglycaemia, and where

data were present, the event rates were too low to yield clinically meaningful interpretation; as such, a meta-analysis for severe hypoglycaemia was not conducted. However, it is important to note that the outcome "hypoglycaemia" reported in this article also included "severe hypoglycaemia".

It is pertinent that we acknowledge the effect that insulin titration may have had on the results for hypoglycaemia. The impact of insulin titration was most apparent in the RCT conducted by D'Alessio et al.[36] which compared once-daily liraglutide 1.8 mg and insulin glargine with an aggressive up-titration of insulin glargine that resulted in a mean insulin dose of 52 units/d at study end (Table S1, Supporting Information) coupled with the down-titration of background SU. The result of the meta-analyses for this comparison show glycaemic control in favour of insulin glargine, a greater increase in weight from baseline and an increased risk of hypoglycaemia which may be a result of aggressive insulin titration. In contrast, the mean doses of insulin glargine in the once-weekly exenatide 2 mg LAR studies used in the pairwise meta-analysis for hypoglycaemia were only 16 to 31 insulin units (Table S1, Supporting Information), which may have been responsible for, not only the lower risk of hypoglycaemia, but also the lesser weight gain and lower HbA1c drop with insulin glargine.[33] It is important to point out that the titration of basal insulin, even in the setting of clinical trials designed around insulin titration, is often suboptimal. For example, in the treat-to-target trial comparing once-daily insulin glargine with NPH insulin, the average dose of insulin was 47.2 IU (SD = 1.3) for glargine and 41.8 IU (SD = 1.3) for NPH.[41] Inadequate insulin dosing could also have implications for a real-world setting, where basal insulin titration might not always occur as it should. As such, GLP-1RAs, some of which do not require any dose titration, could offer a reasonable alternative to basal insulin.

Although our analysis attempted to minimize heterogeneity among studies by ensuring that treatment regimens and outcome time points were consistent, and the systematic review eligibility criteria specifying that background therapy must be received concurrently with study medication, any OAD was allowed as background therapy. However, because of the limited evidence base, heterogeneity was observed among studies, leading to uncertainty concerning the estimates. Table 1 clearly indicates that background therapy varied among the included studies, which could also have impacted the results. Whilst MET is largely weight neutral and has a low risk of hypoglycaemia associated with it, both SU and TZD treatments are associated with weight gain, which should be considered when interpreting results. In addition, SUs carry a moderate risk of hypoglycaemia, which is of particular importance because basal insulin is also associated with weight gain and an increased risk of hypoglycaemia.[42] Although sensitivity analyses can be conducted to assess the impact of differing background therapies, it was not possible in this study because most meta-analyses included only 2 trials, a number insufficient for a meaningful sensitivity analysis.

As the analyses for the present study were being conducted, a systematic review and meta-analysis of once-weekly GLP-1 RAs was published.[10] However, the current study has several important differences from that study and other previously published analyses. Our research question was more specific than that posed by previous analyses. First, we considered only head-to-head comparisons with basal insulins rather than with any antihyperglycemic treatment, which offers more comprehensive evidence for clinicians regarding choice between the two injectable options in the treatment pathway. Second, rather than being restricted to once-weekly GLP-1 Ras, our analysis considered all licensed dosages of all GLP-1 RAs currently being used in clinical practice. And finally, our analysis did not pool drugs according to class; thus, each drug and dosage was considered independently and we pooled only outcome data from studies within the time frame of 16 to 36 weeks of treatment. Although these restrictions meant that some treatments were not included in the meta-analysis, notably albiglutide 30 mg (uptitrated to 50 mg as needed), dulaglutide 1.5 mg (where only one study comparing it to basal insulin at this dose was available) and lixisenatide 20 μg, it was not thought appropriate to conduct an analysis pooling the drugs, dosages or different time frames because head-to-head trials of GLP-1 RAs have demonstrated differences within the class.[43] Another recently published pairwise and network meta-analysis sought to understand the benefits and harms of once-weekly GLP-1 RAs.[16] However, that analysis considered only once-weekly GLP-1 RAs and was conducted primarily to assess the cardiometabolic efficacy and adverse effects of GLP-1 RAs and not the comparison to basal insulin in the treatment paradigm,[16] as we did in our study.

There are several limitations in the current systematic literature review and meta-analysis that should be acknowledged. One limitation is that only English-language articles were searched and included. Although we do not envision the number of included articles to substantially increase if the scope of the search was expanded to include non-English articles, we cannot be certain of the impact of an expanded scope on the results of the meta-analysis. In addition, we combined the results of trials at 26 weeks (±10 weeks) and therefore are unable to draw conclusions about the long-term efficacy and safety of GLP-1 RAs compared to basal insulin; future studies should explore this area. Further, a priori, we developed a protocol to analyse the results of the systematic review by meta-analysis. As future studies are published, expanding the evidence base for GLP-1 RAs compared to basal insulin, consideration of conducting an analysis including both direct and indirect data by network meta-analysis may be warranted.

The meta-analysis conducted for hypoglycemia should be interpreted with caution because of high heterogeneity in defining hypoglycaemic events, an inherent problem when conducting meta-analyses in diabetes.[40] Of the 15 studies identified by the systematic review, the definitions of hypoglycaemia varied considerably (Table S5, Supporting Information). With the exception of the study by Davies et al.[30] which required only the presence of symptoms for a hypoglycaemic event to be reported, the remaining studies did define a hypoglycaemic event using a blood glucose target, but this target varied between 3.0 and 4.0 mmol/L depending on the study. Interpretation of findings from the meta-analysis of hypoglycaemia was further complicated by heterogeneity among studies with regard to background therapies and insulin titration; as such, future trials with similar background therapies, insulin titration algorithms and standardized definitions of hypoglycaemia are warranted for comparability of studies.

In conclusion, the current analysis indicates that once-weekly GLP-1 Ras, exenatide LAR and dulaglutide, demonstrate a greater reduction in HbA1c compared to basal insulin after 26 weeks of treatment. Once- or twice-daily GLP-1 RAs, liraglutide and exenatide, also demonstrate a reduction in HbA1c, but these changes were similar to those seen with basal insulin. Treatment with all GLP-1 RAs results in significant reduction in bodyweight as compared to basal insulins. However, clarity and consistency is required in defining hypoglycaemia in clinical trials, to allow meaningful conclusions to be inferred for this outcome when comparing GLP-1 RAs with basal insulin.

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SUPPORTING INFORMATION

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