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 antihyperglycemic 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. Various diabetes treatment algorithms include GLP-1 RAs as a therapy option after initial treatment with metformin (MET). 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.

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. 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, they all have limitations to consider. Wang et al. do not include the two new agents (dulaglutide and albiglutide) and, although Karagiannis et al. include the new treatments, their analysis is limited to only once-weekly GLP-1 RAs. Liu et al. 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. More recently, Zaccardi et al. 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 pharmacodynamic 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 glycemic 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]) 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-naive 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 (±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. A risk assessment of bias was performed for each included RCT using the Cochrane Collaboration’s tool. 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 I² 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), I² value was also reported. Codes designed for meta-analyses and their outputs were validated by a second analyst.

### 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.
| Trial name and author | Study duration (weeks) | Intervention | Mean age (SD), years | Mean White, % | Mean disease duration (SD), years | Mean HbA1c (SD), % | Mean HbA1c (mmol/mol) | Mean bodyweight (SD), kg | Mean BMI (SD), kg/m² | Background therapy, % |
|----------------------|------------------------|--------------|----------------------|---------------|----------------------------------|--------------------|-----------------------|------------------------|------------------------|-----------------------|
| **Exenatide 10 μg twice daily vs insulin glargine** | | | | | | | | | | |
| Bunck 2009 | 52 | Exenatide | 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 (-) | Double/triple therapy MET ± SU ± TZD |
| 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) | MET (100%) |
| 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 | 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 | 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 (4%-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 | 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 | 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 | 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 | 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 | 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 | 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 + SU³ |
| 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-1 (Gough 2014, 2015) | 52 | Liraglutide | 55.0 (10.2) | 50.0 | 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 | 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 | 8.9 (6.5) | 8.3 (0.9) | 67 | 95.1 (19.7) | 34.9 (4.4) | MET + SU (82%) |
| Glargine | | 54.7 (9.8) | 45.2 | 8.4 (5.7) | 8.4 (1.0) | 68 | 94.6 (19.1) | 33.2 (5.4) | |
| 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, % |
|-------------------------------|-----------------------|--------------|----------------------|-----------|---------|-----------------------------------|-------------------|----------------------|----------------------------|------------------------|-----------------------|
| **Dulaglutide once weekly vs insulin glargine** | | | | | | | | | | |
| 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 | 0² | 8.9 (6.7) | 8.1 (0.8) | 65 | 70.9 (13.7) | 26.1 (5.6) | MET ± SU⁴ |
| | | Glargine | 56.1 (11.3) | 26.0 | 0² | 8.8 (6.1) | 8.0 (0.9) | 64 | 71.1 (13.8) | 25.9 (3.9) | |
| **Lixisenatide versus insulin glargine** | | | | | | | | | | |
| 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 |
| | | 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, lixisenatide 1.8 mg, albiglutide 30 mg (up titrated 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 bodyweight 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 lixisenatide 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 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; I² = 0%) (+0.01 mmol/L [95% CI, −1.2, 1.4]) with exenatide 10 μg, −0.31% (95% CI, −0.42, −0.19; I² = 75%) (−3.4 mmol/L [95% CI, −4.6, −2.1]) with exenatide 2 mg LAR, +0.06%, (95% CI, −0.06, 0.18; I² = 86.1%) (+0.7 mmol/L [95% CI, −0.7, 2.0]) with lixisenatide 1.8 mg and −0.39% (95% CI, −0.49, −0.29; I² = 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; I² = 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.

### 3.3 | 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; I² = 33.2%) with exenatide 2 mg LAR and 0.40 (95% CI, 0.32, 0.51; I² = 96%) with lixisenatide 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.
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 and 5 studies reported no events in one arm. 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, 5 trials of dulaglutide 0.75 mg vs insulin glargine, 2 trials of liraglutide 1.8 mg vs insulin glargine, and 2 trials of dulaglutide 0.75 mg vs insulin glargine. 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.

The 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. 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 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.
−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.35 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 albigrutide 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, 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 hypoglycaemia 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.

ACKNOWLEDGMENTS
We thank James Eaton for study planning and Sarah Goring (both of ICON Plc) for analysis validation and manuscript editing.

Conflict of interest
S. S. has served previously on the Advisory Board of Eli Lilly and was compensated for his time. E. E. W. has served previously on a speaker's bureau for Eli Lilly, Boehringer Ingelheim and Abbott Diabetes Care, on advisory boards for Eli Lilly, Boehringer Ingelheim, Abbott Diabetes Care, Amgen and Voluntis, and as a consultant for Eli Lilly, Boehringer Ingelheim, Abbott Diabetes Care and Amgen, and has received grants from Abbott Diabetes Care. A. K. and R. J. are employees of Lilly USA, LLC and are Lilly stock holders. M. Y. is an employee of Eli Lilly Canada Inc. and is a Lilly stock holder. J. T., I. S., E. K. and N. W. are employees of the consultancy group of ICON plc, which received compensation for the completion of the analysis.

Author contributions
S. S. participated in the conception, design, analysis, and interpretation of drafting the results of the manuscript. He did not receive any compensation for his participation in the study. E. E. W. participated in the original study design, analysis of the data, and review and editing of the manuscript. He did not receive any compensation for his participation in the study. A. K., and R. J. contributed to the design of the study, analysis of the data and review and editing of the paper. M. Y. contributed to the design of the study, analysis of the data and review and editing of the paper. J. T., I. S., E. K. and N. W. participated in the conception, design, interpretation and writing of the manuscript.

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How to cite this article: SINGH ET AL. 2015. Diabetes Care. 2015;38(12):2241-2249.