



# Efficacy and Safety of Short- and Long-Acting Glucagon-Like Peptide 1 Receptor Agonists on a Background of Basal Insulin in Type 2 Diabetes: A Meta-analysis

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## PURPOSE

To compare the efficacy and safety of short- and long-acting glucagon-like peptide 1 receptor agonists (GLP-1 RAs), both used in combination with basal insulin, in patients with type 2 diabetes.

## DATA SOURCES AND STUDY SELECTION

Randomized controlled trials comparing the coadministration of short- or long-acting GLP-1 RAs and basal insulin with basal insulin  $\pm$  placebo were identified (PubMed search). Of 974 identified publications, 14 clinical trials were included. Eight trials examined short-acting and six long-acting GLP-1 RAs.

## DATA EXTRACTION AND DATA SYNTHESIS

Differences in HbA<sub>1c</sub>, fasting plasma glucose, body weight, and adverse events were compared between studies using short- or long-acting GLP-1 RAs by random-effects meta-analysis.

## LIMITATIONS

There were relatively small numbers of available publications, some heterogeneity regarding protocols, and differences in the GLP-1 RA compound used.

## CONCLUSIONS

Long-acting GLP-1 RAs more effectively reduced HbA<sub>1c</sub> ( $\Delta$   $-6$  mmol/mol [95% CI  $-10$ ;  $-2$ ],  $P = 0.007$ ), fasting plasma glucose ( $\Delta$   $-0.7$  mmol/L [ $-1.2$ ;  $-0.3$ ],  $P = 0.007$ ), and body weight ( $\Delta$   $-1.4$  kg [ $-2.2$ ;  $-0.6$ ],  $P = 0.002$ ) and raised the proportion of patients achieving an HbA<sub>1c</sub> target  $<7.0\%$  ( $<53$  mmol/mol) ( $P = 0.03$ ) more than the short-acting ones. Patients reporting symptomatic ( $P = 0.048$ ) but not severe ( $P = 0.96$ ) hypoglycemia were fewer with long- versus short-acting GLP-1 RAs added to insulin. A lower proportion of patients reported nausea ( $-52\%$ ,  $P < 0.0001$ ) or vomiting ( $-36\%$ ,  $P = 0.0002$ ) with long-acting GLP-1 RAs. Overall, GLP-1 RAs improved HbA<sub>1c</sub>, fasting plasma glucose, and body weight when added to basal insulin. However, long-acting GLP-1 RAs were significantly more effective for glycemic and body weight control and displayed better gastrointestinal tolerability.

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Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are used not only on a background of oral glucose-lowering medications but also in conjunction with basal insulin therapy (1,2). On the basis of their pharmacokinetic properties, short-acting GLP-1 RAs at their recommended injection regimens lead to intermittent exposure, changing between short-lived peaks with troughs characterized by negligible drug concentrations in between (3). Long-acting GLP-1 RAs are characterized by a steadier exposure, with relatively small fluctuations in plasma drug concentrations over a 24-h period (3). The resulting continuous exposure of GLP-1 receptors leads to tachyphylaxis for the deceleration of gastric emptying with prolonged use of GLP-1 RAs (4–7). Since postmeal glycemic excursions are determined by the velocity of gastric emptying (8,9), long-acting GLP-1 RAs in the long run have less of an effect on postprandial glucose increments (3,6,7), while short-acting GLP-1 RAs retain the ability to slow gastric emptying and to cause rather flat postmeal glycemic excursions, even with prolonged treatment (3,6,7).

On a background of oral glucose-lowering agents, long-acting GLP-1 RAs are more effective in controlling HbA<sub>1c</sub>, mainly through their better ability to lower fasting glucose (3,6,10), directly related to overnight exposure to higher drug concentrations compared with short-acting GLP-1 RAs (11). Combinations of basal insulin and GLP-1 RAs have been proposed to act in a synergistic manner, assuming that the basal insulin component will mainly control fasting plasma glucose, while the GLP-1 RA is thought to limit postmeal glycemic increments. Such combinations have been shown to provide an overall glycemic control similar to more complex basal-bolus regimens (12). On the basis of theoretical considerations, it has been assumed that in such combination therapy regimens, short-acting agents should have the advantage of more profoundly affecting postprandial glycemic increments because of their retained action on gastric emptying after long-term exposure. However, while numerous studies have proven the effectiveness of GLP-1 RAs on a background of basal insulin therapy (13–26), none have directly compared a short- with a long-acting compound.

In the absence of head-to-head comparisons, we aimed to compare short- and long-acting GLP-1 RAs when used in

conjunction with basal insulin. Therefore, a meta-analysis of published clinical trials comparing combinations of GLP-1 RAs on a background of basal insulin therapy with basal insulin  $\pm$  placebo was performed, focusing on differences between short- and long-acting compounds regarding their effects on HbA<sub>1c</sub>, fasting plasma glucose, and body weight.

## METHODS

### Search Strategy and Study Selection

For the present analysis, articles reporting clinical trials that compared a combination of GLP-1 RA and basal insulin therapy with basal insulin  $\pm$  placebo were identified through a systematic PubMed search. The search terms are displayed in Supplementary Table 1. Studies were included if published before 31 December 2018. Of 1,306 records identified initially, 14 publications could be used (13–26), with 8 reporting on a combination of short-acting GLP-1 RAs (13–20) and 6 reporting on long-acting GLP-1 RAs plus basal insulin (21–26). Exclusion criteria are described in Supplementary Fig. 1 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (27). Open-label and blinded randomized prospective studies were eligible if they studied free or fixed-dose combinations of GLP-1 RAs and basal insulin in patients with type 2 diabetes. We selected studies reporting baseline and end-of-study HbA<sub>1c</sub>, fasting plasma glucose, and body weight as well as adverse events, prevalence of hypoglycemia, and proportion of patients prematurely discontinuing drug treatment. The minimum duration was 6 weeks. Two studies reporting on GLP-1 RAs on a background of premixed insulin preparations in a small subgroup were also included (14,15). We registered our protocol with PROSPERO (<https://www.crd.york.ac.uk/prospéro/>; identification No. CRD42019126069).

### Design of the Analysis

Reductions in HbA<sub>1c</sub>, fasting plasma glucose, and body weight (study end vs. baseline) were compared between GLP-1 RA plus basal insulin and basal insulin  $\pm$  placebo. These differences were subjected to a random-effects meta-analysis, with subgroups defined using short- or long-acting GLP-1 RAs (Comprehensive Meta-Analysis version 3; <https://www.meta-analysis.com>). Changes in HbA<sub>1c</sub>

were defined as the primary end point. Changes in HbA<sub>1c</sub> target achievement ( $<7.0\%$  and  $\leq 6.5\%$ ), fasting plasma glucose, and body weight were secondary end points. Safety end points included adverse events, hypoglycemia, and premature discontinuation.

### Quality Assessment

Study quality was assessed by applying the Jadad score (28) (Supplementary Table 2) and the Risk of Bias tool (<https://www.riskofbias.info>) (29) (Supplementary Fig. 2). All publications were suitable for our analysis.

### Data Extraction

Relevant data were extracted into pre-structured paper forms listing variables of interest (Supplementary Material). Data were extracted by J.A.H. In case of questions, M.A.N. was consulted. In case of differences that could not be resolved, J.J.M. had the final decision. The way how gastrointestinal adverse events have been captured has systematically been categorized as shown in Supplementary Table 3.

### Data Synthesis and Meta-analysis

For the main end points (HbA<sub>1c</sub>, fasting plasma glucose, body weight reduction), the differences between study end and baseline with their 95% CIs were analyzed. Differences resulting from treatment with the combination of GLP-1 RAs and basal insulin and those obtained with basal insulin  $\pm$  placebo were subjected to random-effects meta-analysis. Subgroups were studies using short- or long-acting GLP-1 RAs. Output variables were differences in means (to insulin  $\pm$  placebo). The subgroups were further compared by calculating their difference as well as pooled SD (30,31) from which the 95% CIs were derived and *P* values calculated by unpaired Student *t* tests (common SD) or by Welch *t* test (substantially different SDs) (32). *Z* values, *P* values, and the weight of single studies in the overall analysis were obtained for each study as well as for the subgroups and all GLP-1 RAs pooled. Heterogeneity was reported as *Q* value, *I*<sup>2</sup>, and  $\tau^2$ . Reporting biases were assessed using a funnel plot and further analyzed with Egger regression intercept (33) and the trim-and-fill method of Duval and Tweedie (34). Graphs derived from the meta-analysis were redrawn using GraphPad Prism version 8.0.0

software (<https://www.graphpad.com>) to allow the use of various colors.

### Sensitivity Analyses

To test for robustness and potential causes of heterogeneity, the following sensitivity analyses were performed: Main results were recalculated for studies either titrating insulin during the study or not, for studies with a duration of <28 weeks and ≥28 weeks, with different sizes of patient numbers (small [ $n = 259$ – $323$ ], intermediate [ $n = 398$ – $495$ ], large [ $n = 731$ – $1,246$ ]), and for studies using free or fixed-dose combinations.  $P$  values for interaction were calculated for each comparison. In addition, we systematically studied all major efficacy and safety results for robustness by repeating all analyses with one study after the other eliminated from the calculations.

### Regression Analyses

A linear regression analysis was performed relating changes in fasting plasma glucose and HbA<sub>1c</sub> as well as reductions in postmeal glycemic excursions and HbA<sub>1c</sub> to test for an association in improving glycemic control. Postmeal glycemic excursions were derived from self-monitoring of plasma glucose profiles. Differences between premeal and postmeal measurements were averaged across the three main meals of the day.

### Statistical Analysis

Baseline patient characteristics and results at study end are reported as mean ± SD or counts (percentages). Pooled mean values and SDs for all studies belonging to the subgroups using short- and long-acting GLP-1 RAs were calculated using standard equations. Results of the meta-analysis are reported as differences between baseline and study end and between GLP-1 RA plus basal insulin treatment and basal insulin ± placebo and their 95% CIs. Significances of differences were tested by using unpaired Student and Welch  $t$  test.  $P < 0.05$  was taken to indicate significant differences.

## RESULTS

### Selection of Publications

Eight publications used in the present analysis regarded short-acting GLP-1 RAs, and six concerned long-acting GLP-1 RAs. Relatively more studies on lixisenatide and fixed-dose combination of lixisenatide and insulin glargine (iGlarLixi) were

available than those for any of the long-acting GLP-1 RAs (Supplementary Table 1 and Supplementary Fig. 1).

### Quality Assessment

The quality of the studies assessed by the Jadad score (28) (Supplementary Table 2) and the Risk of Bias tool (29) (Supplementary Fig. 2) was found to be sufficient for the inclusion of all retrieved publications.

### Study Characteristics

Table 1 informs about the individual design of studies used in the present meta-analysis.

### Baseline Characteristics

Baseline patient characteristics of all studies analyzed are shown in Supplementary Tables 4–7. Further study protocol details are shown in Supplementary Tables 8 and 9.

### Primary End Point

All studies analyzed indicated a significant reduction in HbA<sub>1c</sub> with GLP-1 RAs plus basal insulin versus basal insulin ± placebo (Fig. 1A). This resulted in overall significant differences when looking not only at all GLP-1 RAs ( $\Delta -0.7\%$  [95% CI  $-1.2$ ;  $-0.2$ ],  $-8$  mmol/mol [ $-13$ ;  $-2$ ],  $P = 0.006$ ) but also for the subgroups of short-acting ( $\Delta -0.5\%$  [ $-0.7$ ;  $-0.3$ ],  $-5$  mmol/mol [ $-7$ ;  $-3$ ],  $P < 0.0001$ ) and long-acting ( $\Delta -1.0\%$  [ $-1.2$ ;  $-0.8$ ],  $-11$  mmol/mol [ $-13$ ;  $-8$ ],  $P < 0.0001$ ) GLP-1 RAs (Fig. 1A).

### Secondary End Points

#### HbA<sub>1c</sub> Target Achievement

The difference in proportions of patients achieving an HbA<sub>1c</sub> <7.0% (<53 mmol/mol) (Fig. 1B) or ≤6.5% (<48 mmol/mol) (Supplementary Fig. 3) was significantly greater for long-acting GLP-1 RAs.

#### Fasting Plasma Glucose

Nearly all studies using long-acting GLP-1 RAs reported a significant reduction in fasting plasma glucose compared with administration of basal insulin ± placebo, while for most short-acting GLP-1 RAs, no significant reduction was observed (Fig. 1C). This resulted in overall insignificant differences when looking at all GLP-1 RAs ( $\Delta -0.5$  mmol/L [95% CI  $-1.2$ ;  $0.2$ ],  $P = 0.18$ ) and short-acting GLP-1 RAs ( $\Delta -0.1$  mmol/L [ $-0.4$ ;  $0.2$ ],  $P = 0.35$ ) but in a highly significant difference for the long-acting GLP-1

RAs ( $\Delta -0.9$  mmol/L [ $-1.2$ ;  $-0.5$ ],  $P < 0.0001$ ) (Fig. 1C).

### Body Weight

Body weight was almost uniformly reduced in most studies except for one using lixisenatide (Fig. 1C). The effect for all GLP-1 RAs was significant ( $\Delta -2.0$  kg [95% CI  $-3.4$ ;  $-0.6$ ],  $P = 0.005$ ), as was the effect in both subgroups representing short-acting ( $\Delta -1.3$  kg [ $-1.7$ ;  $-0.8$ ],  $P < 0.0001$ ) and long-acting ( $\Delta -2.7$  kg [ $-3.3$ ;  $-2.1$ ],  $P < 0.0001$ ) GLP-1 RAs. Semaglutide had the largest effect on body weight, again explaining some of the observed heterogeneity.

### Association in Reduction of HbA<sub>1c</sub> With Changes in Fasting and Postmeal Plasma Glucose

As depicted in Supplementary Fig. 4A, there was a significant association of the reduction in fasting plasma glucose and HbA<sub>1c</sub> reduction for all GLP-1 RAs, which fell almost on the same regression line ( $P = 0.94$  and  $P = 0.99$  for potential differences in the slope and y-axis intercept of the regression lines). Short-acting GLP-1 RA studies resulted in smaller reductions in both fasting plasma glucose and HbA<sub>1c</sub> compared with long-acting GLP-1 RAs.

The association between reductions in postmeal glycemic excursions and HbA<sub>1c</sub> was different. While the distribution of postprandial glucose increment reduction was similar for short- and long-acting GLP-1 RAs, its impact on HbA<sub>1c</sub> reduction was considerably stronger in the case of long-acting GLP-1 RAs, as indicated by a significant difference in the y-axis intercept ( $P = 0.0033$ ) (Supplementary Fig. 4B).

### Differences Among Subgroups

Long-acting GLP-1 RAs had significantly greater effects on HbA<sub>1c</sub> reduction ( $\Delta -0.5\%$  [95% CI  $-0.9$ ;  $-0.2$ ],  $-5.8$  mmol/mol [ $-9.6$ ;  $-2.0$ ],  $P = 0.007$ ) (Fig. 2A), fasting plasma glucose reduction ( $\Delta -0.7$  mmol/L [ $-1.2$ ;  $-0.3$ ],  $P = 0.007$ ) (Fig. 2C), and body weight reduction ( $\Delta -1.4$  kg [ $-2.2$ ;  $-0.6$ ],  $P = 0.002$ ) (Fig. 2D), all compared with insulin ± placebo, versus short-acting GLP-1 RAs. They were also more effective in the achievement of HbA<sub>1c</sub> targets (<7.0% [53 mmol/mol]:  $\Delta 18.6$  [10.6;  $-31.7$ ],  $P = 0.03$  [Fig. 2D]; ≤6.5% [48 mmol/mol]:  $\Delta 21.2$  [10.6;  $31.7$ ],  $P = 0.001$  [Fig. 2B and Supplementary Fig. 3]).

**Table 1—Overview of the individual design of studies used for the present meta-analysis comparing the efficacy and safety of short- and long-acting GLP-1 RAs in combination with basal insulin**

Study	Publication year	Trial duration (weeks)	GLP-1 RA	Basal insulin	Use of placebo	Combination of GLP-1 RA and basal insulin	Study design	Titration of basal insulin during trial	Target dose of GLP-1 RA
<b>Short-acting GLP-1 RAs added to basal insulin</b>									
Buse et al. (13)	2011	30	Exenatide (twice a day)	Insulin glargine	Yes	Free	Double blind	Yes	20 µg/day
Seino et al. (14)	2012	24	Lixisenatide	Basal insulin <sup>a</sup>	Yes	Free	Double blind	No	20 µg/day
Riddle et al. (15)	2013	24	Lixisenatide	Basal insulin <sup>a</sup>	Yes	Free	Double blind	No	20 µg/day
Riddle et al. (16)	2013	24	Lixisenatide	Insulin glargine	Yes	Free	Double blind	Yes	20 µg/day
Yang et al. (17)	2018	24	Lixisenatide	Basal insulin <sup>a</sup>	Yes	Free	Double blind	No	20 µg/day
Aroda et al. (18)	2016	30	Lixisenatide	Insulin glargine	No	Fixed (iGlarLixi)	Open label	Yes	5–20 µg/day <sup>b</sup>
Rosenstock et al. (19)	2016	30	Lixisenatide	Insulin glargine	No	Fixed (iGlarLixi)	Open label	Yes	5–20 µg/day <sup>b</sup>
Rosenstock et al. (20)	2016	24	Lixisenatide	Insulin glargine	No	Fixed (iGlarLixi)	Open label	Yes	5–20 µg/day <sup>b</sup>
<b>Long-acting GLP-1 RAs added to basal insulin</b>									
Ahmann et al. (21)	2015	26	Liraglutide	Basal insulin <sup>a</sup>	Yes	Free	Double blind	No	1.8 mg/day
Guja et al. (22)	2018	28	Exenatide (once a week)	Insulin glargine	Yes	Free	Double blind	Yes	2.0 mg/week
Pozzilli et al. (23)	2017	28	Dulaglutide	Insulin glargine	Yes	Free	Double blind	Yes	1.5 mg/week
Rodbard et al. (24)	2018	30	Semaglutide	Basal insulin <sup>a</sup>	Yes	Free	Double blind	No	1.0 mg/week
Buse et al. (25)	2014	26	Liraglutide	Insulin degludec	No	Fixed (iDegLira)	Double blind	Yes	0.6–1.8 mg/day <sup>b</sup>
Gough et al. (26)	2014	26	Liraglutide	Insulin degludec	No	Fixed (iDegLira)	Open label	Yes	0.36–1.8 mg/day <sup>b</sup>

<sup>a</sup>Different compounds of basal insulin were used; a detailed presentation is given in Supplementary Tables 6 and 8. <sup>b</sup>As per result of the titration process.

## Insulin Doses

In combination with GLP-1 RAs, the insulin dose at the end of titration was lower than with basal insulin alone (Supplementary Table 5). This difference was more marked and significant in the case of long-acting GLP-1 RAs. In studies using fixed-dose combinations, such differences were less apparent, probably related to protocol-related maximum limits for insulin doses (Supplementary Table 6).

## Adverse Events

Nausea, vomiting, and diarrhea were reported in a small proportion of those treated with insulin  $\pm$  placebo but occurred with greater prevalence in those treated by GLP-1 RAs with basal insulin (Table 2). Among patients treated with GLP-1 RAs and basal insulin, the proportion with nausea was approximately twofold higher in the case of short-acting GLP-1 RAs ( $P < 0.0001$ ). Vomiting was observed more frequently (57%) with short-acting GLP-1 RAs ( $P < 0.0001$ ) as well. There were no major differences regarding diarrhea (Table 2).

## Hypoglycemia

The proportion of patients reporting symptomatic hypoglycemia was higher in patients treated with GLP-1 RAs and basal insulin than in those treated with basal insulin  $\pm$  placebo ( $P = 0.020$ ) (Supplementary Table 10). Patients treated in studies using short-acting GLP-1 RAs and basal insulin had slightly higher proportions reporting symptomatic hypoglycemic episodes compared with those using long-acting GLP-1 RAs (27.3 vs. 24.4%,  $P = 0.048$ ) (Supplementary Table 10). Proportions of patients reporting severe episodes of hypoglycemia were low and not significantly different between studies using short- and long-acting GLP-1 RAs (Supplementary Table 10).

## Sensitivity Analyses

Results regarding differences in HbA<sub>1c</sub>, fasting plasma glucose, and body weight reduction as well as achievement of HbA<sub>1c</sub> target remained consistent with various sensitivity analyses (Supplementary Fig. 5A–D). Only one comparison related to fasting plasma glucose showed a significant  $P$  value for interaction between studies with active insulin titration versus constant insulin doses. In line with a previous meta-analysis (35), there was no significant or substantial difference

between free and fixed-dose combinations of GLP-1 RAs and basal insulin. If the subgroups are again divided into subgroups and an analysis is performed separately, the difference between short- and long-acting GLP-1 RAs stays significant for the main end points when only the free combinations are compared, but there is no significant difference when short- and long-acting GLP-1 RAs are compared as components of fixed-dose combinations (insulin glargine and lixisenatide [iGlarLixi] vs. insulin degludec and liraglutide [iDegLira]) (Supplementary Table 11). Systematically eliminating studies from the analysis did not at all change the interpretation regarding all efficacy parameters. Likewise, for nausea, vomiting, and symptomatic hypoglycemia as main adverse events, our conclusions were fully confirmed. Regarding diarrhea and severe hypoglycemia, differences between short- and long-acting GLP-1 RAs remained nonsignificant like in the full analysis (Supplementary Tables 12–15).

## Publication Bias

The funnel plot and the Egger regression intercept (33) ( $P = 0.005$ ) indicate some degree of publication bias, but using the method of Duval and Tweedie (34), only one study is trimmed with very small and insignificant effects ( $P = 0.75$ ) (Supplementary Fig. 6). So, even if there had been publication bias, it should not have had a great impact on the overall results regarding our main end point.

## DISCUSSION

The present meta-analysis comparing short- and long-acting GLP-1 RAs on a background of basal insulin therapy was driven by the hypothesis that a more pronounced effect on preventing post-meal glycemic excursions of short-acting GLP-1 RAs might potentially outweigh a greater effect on fasting plasma glucose of long-acting GLP-1 RAs (3,7,11). Our results clearly indicate that in combination with basal insulin, long-acting GLP-1 RAs resulted in greater reductions in HbA<sub>1c</sub>, fasting plasma glucose, and body weight (Fig. 1). This is novel information not available from previous meta-analyses (35–37) and provides meaningful guidance for the choice of GLP-1 RAs to be used in combination with basal insulin.

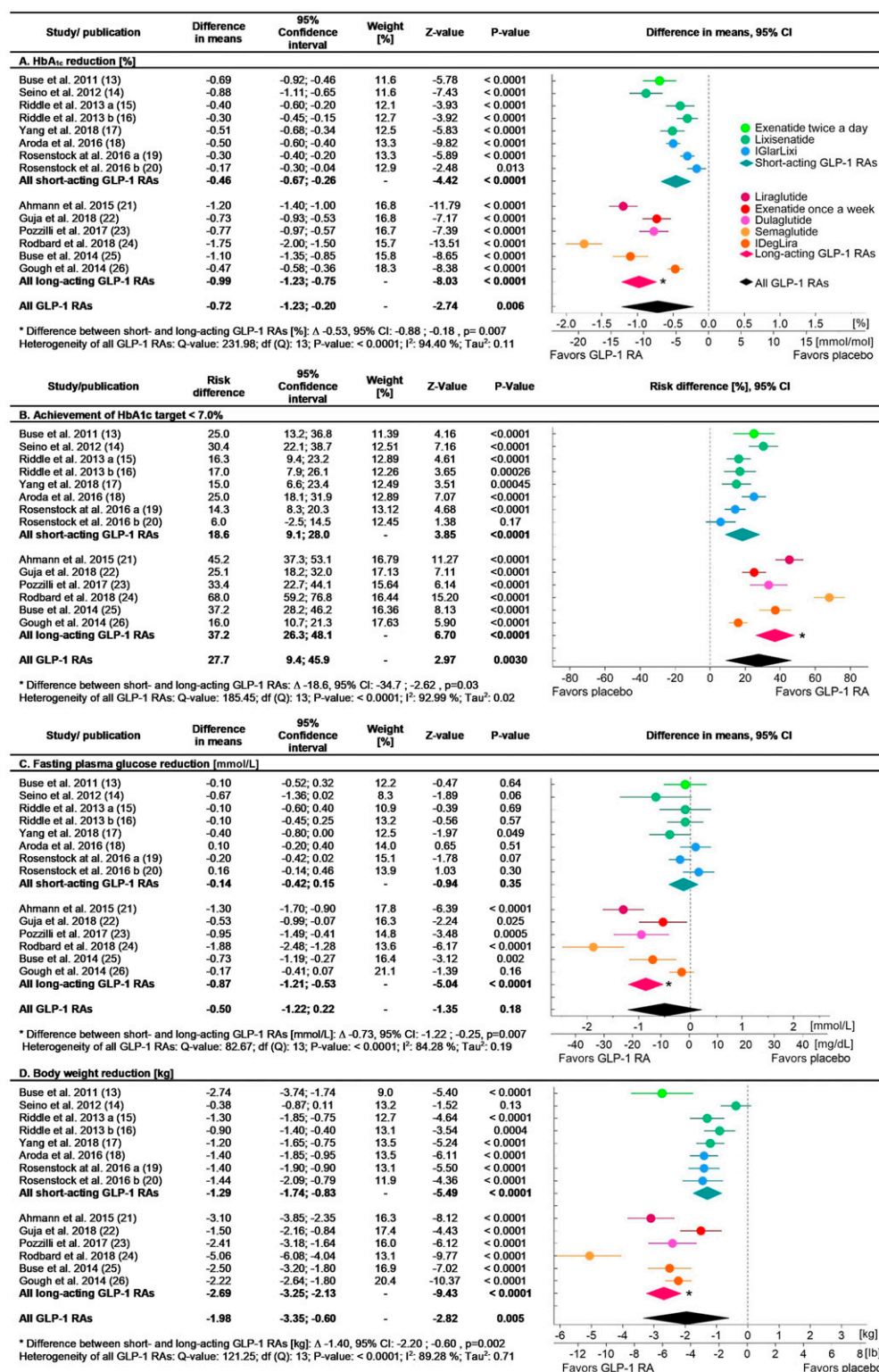
The results regarding HbA<sub>1c</sub> and fasting plasma glucose reduction resemble

previous findings in clinical trials comparing short- with long-acting GLP-1 RAs on a background of oral glucose-lowering medications (6,38,39). The explanation for the greater efficacy of long-acting GLP-1 RAs has been the greater exposure to drug concentrations during the overnight period with an associated greater reduction in overnight and early morning fasting plasma glucose concentrations (3).

The selection of studies on a combination of short-acting GLP-1 RAs and basal insulin was such that only one study with exenatide twice a day contrasts with seven studies using lixisenatide. Exenatide twice a day seems to be particularly different in its ability to reduce body weight (Fig. 1D). Overall, our results regarding short-acting GLP-1 RAs combined with basal insulin mainly inform about lixisenatide.

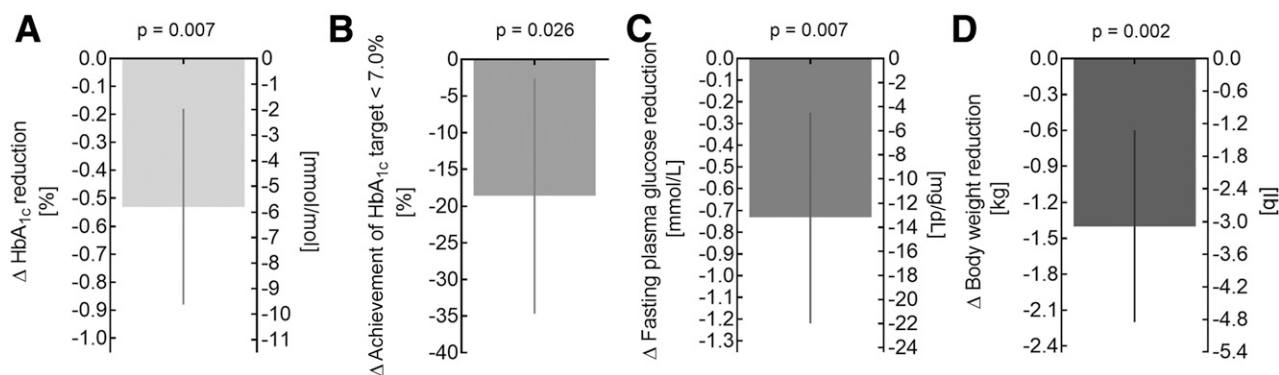
Previous meta-analyses have underscored the efficacy of a combination of GLP-1 RAs and basal insulin (37) without differentiating the effects of short- versus long-acting compounds within the GLP-1 RA class. For example, free combinations of a GLP-1 RA with basal insulin have been compared with fixed-dose combinations (35), and no essential differences in effectiveness on HbA<sub>1c</sub> or body weight reduction were found (35). Like in our analysis (Supplementary Fig. 5 and Supplementary Table 11), no significant differences in the efficacy regarding absolute HbA<sub>1c</sub> or body weight reductions between iGlarLixi and iDegLira were described in a previous publication (36).

A novel aspect of the present analysis is that this effect on fasting plasma glucose is observed in studies allowing basal insulin use (and in some studies, titration) in the comparator group. This indicates that there is an additional lowering of overnight and early morning fasting plasma glucose with long-acting GLP-1 RAs, even on top of basal insulin. Thus, the fasting plasma glucose level reached was not significantly different between patients treated with short-acting GLP-1 RAs plus basal insulin compared with basal insulin  $\pm$  placebo, while there was a significant difference for long-acting GLP-1 RAs (Fig. 1 and Supplementary Table 5). As indicated by the regression analysis, the additional reduction in fasting plasma glucose concentrations induced by long-acting GLP-1 RAs seems to have an important role in mediating the improvement in overall glycemic control (Supplementary Fig. 4A).



**Figure 1**—Forest plot of reductions in HbA<sub>1c</sub> (A), the proportion of patients achieving an HbA<sub>1c</sub> target < 7.0% (B), and reductions in fasting plasma glucose (C) and body weight (D) in patients with type 2 diabetes treated with short- or long-acting GLP-1 RAs in combination with basal insulin. Forest plots show the difference in means (A, C, and D) and the risk difference (B) between the intervention arm (GLP-1 RA + basal insulin) and comparator arm (placebo + basal insulin or basal insulin alone). Color codes for the various GLP-1 RAs are shown in panel A. Filled circles indicate the results for individual studies, while rhombuses indicate results of the meta-analysis. Measures of heterogeneity are also shown in all panels (Q,  $I^2$ ,  $\tau^2$ , and related P values) for all GLP-1 RAs. A detailed presentation of the heterogeneity statistics for the subgroups of short- and long-acting GLP-1 RAs is provided in Supplementary Table 17.





**Figure 2**—Differences in reductions in HbA<sub>1c</sub> (A), the proportion of patients achieving an HbA<sub>1c</sub> target <7.0% (B), and reductions in fasting plasma glucose (C) and body weight (D) relative to placebo/insulin only between short- and long-acting GLP-1 RAs added to basal insulin therapy. Mean differences and their 95% CIs are shown. *P* values were calculated on the basis of the comparison of subgroups (short- vs. long-acting GLP-1 RAs) that was based on the meta-analysis as depicted in Fig. 1.

The lack of HbA<sub>1c</sub> differences in favor of short-acting GLP-1 RAs versus long-acting GLP-1 RAs in combination with basal insulin (Supplementary Fig. 4B) may be explained by the finding that differences in postmeal increments in plasma glucose concentrations between patients treated with GLP-1 RAs plus basal insulin and those treated with basal insulin only were relatively small ( $\sim 0.5$  mmol/L at peak and only representative for limited periods after meals) (Supplementary Fig. 4B). Furthermore, this reduction in postprandial glycemic rises only applies to limited meals, before a short-acting GLP-1 RA has been injected. This may explain why the postprandial effects of short-acting GLP-1 RAs do not quantitatively impact much on HbA<sub>1c</sub> reductions, while the reduction in fasting plasma glucose following long-acting GLP-1 RA treatment ( $\sim 0.65$  mmol/L) (Supplementary Fig. 4A) is of greater magnitude and can be assumed to be maintained for a much longer period during the night and in the morning. Additional reasons may include the ability of basal insulin treatment itself to reduce postprandial increments in glucose concentrations, especially when near-normal targets for fasting plasma glucose are reached (40).

The greater reduction in body weight found with long- rather than short-acting GLP-1 RAs used on background of basal insulin is at variance with studies using GLP-1 RAs together with oral glucose-lowering medications (6,38,39). Previous publications have not described a difference between short- and long-acting GLP-1 RAs in this respect (6,38,39,41). Thus, concomitant insulin therapy seems

to modify weight-reducing effects of GLP-1 RAs, perhaps related to its effect on glucosuria (42). The differences in insulin doses reached after titrating basal insulin alone or in combination with GLP-1 RAs (Supplementary Tables 8 and 9) most likely has affected the results regarding body weight (Figs. 1 and 2) and hypoglycemic episodes (Supplementary Table 10).

The reduction of gastrointestinal adverse events for studies using long-acting compared with short-acting GLP-1 RAs (Table 2) is in line with previous meta-analyses compiling tolerability data for various GLP-1 RAs on a variety of background glucose-lowering medications, including basal insulin (43). As underscored by the different ways of capturing gastrointestinal adverse events (Supplementary Table 3), there is the possibility of heterogeneity across trials with respect to trial-specific definitions and data capture methods, trial time frame, location of trial sites, and other influences. The trend toward more symptomatic hypoglycemic episodes with the combination of GLP-1 RAs and basal insulin versus basal insulin  $\pm$  placebo probably represents the better glycemic control in those treated with the combination. This difference was slightly smaller with long-acting GLP-1 RAs (Supplementary Table 10) and may be related to significantly lower insulin doses when using the combination in the case of long-acting, but not short-acting, GLP-1 RAs (Supplementary Tables 6 and 7).

There are some important differences between using free versus fixed-dose combinations of GLP-1 RAs and basal

insulin. In the case of fixed-dose combinations, there may be a maximum insulin dose-limiting titration (because otherwise, the GLP-1 RA dose would rise above approved dose ranges [18–20,25,26]), and often, such considerations have had an impact on selection criteria for patients participating in such studies (to exclude those with a high insulin requirement). Also, since not all patients on fixed-dose combinations reach the maximum dose, their exposure to GLP-1 RAs, on average, is lower than with free combinations. Otherwise, the differences in the primary outcome were significant when comparing free combinations of short- and long-acting GLP-1 RAs, while this was not the case for fixed-dose combinations, which is in line with a previous meta-analysis (36). The main reason probably is the smaller number of studies with fixed-dose combinations. Nevertheless, we find similar differences between basal insulin alone or in combination with GLP-1 RAs, regardless of the use of free or fixed-dose combinations (Supplementary Table 11). Nonsignificant interaction *P* values suggest that the overall results apply to free and fixed-dose combinations.

Limitations of our study are the relatively small number of publications available, some heterogeneity regarding protocols, and probably most importantly, differences in the GLP-1 RA compound used (pharmacokinetic properties, known clinical effectiveness, free vs. fixed-dose combination affecting the titration process and the final dose used during the core trial period, etc.) (44). Nevertheless, our study had an unequivocal result, and the conclusions seem to be robust, as indicated by various

**Table 2—Overview of adverse events and withdrawals from studies used for the present meta-analysis comparing the efficacy and safety of short- and long-acting GLP-1 RAs in combination with basal insulin**

Study, publication year	Patients, n		Nausea, n (%)		Vomiting, n (%)		Diarrhea, n (%)		Withdrawals because of adverse events, n (%)		Withdrawals because of any reason, n (%)	
	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo
<b>Short-acting GLP-1 RAs added to basal insulin</b>												
Buse et al. (13), 2011	137	122	56 (40.9)	10 (8.2)	25 (18.2)	5 (4.1)	25 (18.2)	10 (8.2)	13 (9.5)	1 (0.8)	26 (19.0)	22 (18.0)
Seino et al. (14), 2012	154	157	61 (39.6)	7 (4.5)	28 (18.2)	3 (1.9)	10 (6.5)	4 (2.5)	14 (9.1)	5 (3.2)	21 (13.6)	13 (8.3)
Riddle et al. (15), 2013	328	167	86 (26.2)	14 (8.4)	27 (8.2)	1 (0.6)	24 (7.3)	9 (5.4)	26 (7.9)	4 (2.4)	53 (16.2)	20 (12.0)
Riddle et al. (16), 2013	223	223	61 (27.4)	11 (4.9)	21 (9.4)	3 (1.3)	15 (6.7)	7 (3.1)	19 (8.5)	9 (4.0)	29 (13.0)	12 (5.4)
Yang et al. (17), 2018	223	223	51 (22.9)	12 (5.4)	25 (11.2)	2 (0.9)	NA	NA	8 (3.6)	4 (1.8)	32 (14.3)	18 (8.1)
Aroda et al. (18), 2016	366	365	38 (10.4)	2 (0.5)	13 (3.6)	2 (0.5)	16 (4.4)	10 (2.7)	12 (3.3)	3 (0.8)	29 (7.9)	10 (2.7)
Rosenstock et al. (19), 2016	468	466	45 (9.6)	17 (3.6)	15 (3.2)	7 (1.5)	42 (9.0)	20 (4.3)	12 (2.6)	9 (1.9)	29 (6.2)	27 (5.8)
Rosenstock et al. (20), 2016	161	162	12 (7.5)	0 (0.0)	4 (2.5)	1 (0.6)	5 (3.1)	6 (3.7)	6 (3.7)	0 (0.0)	11 (6.8)	3 (1.9)
All short-acting GLP-1 RA	2,060	1,885	410 (19.9)	73 (3.9)	158 (7.7)	24 (1.3)	137 (7.5)	66 (4.0)	110 (5.3)	35 (1.9)	230 (11.2)	125 (6.6)
<b>Long-acting GLP-1 RAs added to basal insulin</b>												
Ahmann et al. (21), 2015	225	225	50 (22.2)	7 (3.1)	20 (8.9)	2 (0.9)	24 (10.7)	11 (4.9)	12 (5.3)	3 (1.3)	35 (15.6)	51 (22.7)
Guja et al. (22), 2018	231	230	12 (5.2)	9 (3.9)	1 (0.4)	3 (1.3)	11 (4.8)	8 (3.5)	7 (3.0)	5 (2.2)	19 (8.2)	23 (10.0)
Pozzilli et al. (23), 2017	150	150	18 (12.0)	2 (1.3)	9 (6.0)	0 (0.0)	17 (11.3)	6 (4.0)	6 (4.0)	2 (1.3)	12 (8.0)	16 (10.7)
Rodbard et al. (24), 2018	131	133	22 (16.8)	6 (4.5)	15 (11.5)	4 (3.0)	9 (6.9)	2 (1.5)	10 (7.6)	1 (0.8)	16 (12.2)	13 (9.8)
Buse et al. (25), 2014	199	199	13 (6.5)	7 (3.5)	NA	NA	13 (6.5)	7 (3.5)	1 (0.5)	3 (1.5)	32 (16.1)	35 (17.6)
Gough et al. (26), 2014	833	413	73 (8.8)	15 (3.6)	32 (3.8)	6 (1.5)	66 (7.9)	19 (4.6)	10 (1.2)	8 (1.9)	90 (10.8)	47 (11.4)
All long-acting GLP-1 RAs	1,769	1,350	170 (9.6)*	46 (3.4)	77 (4.9)†	15 (1.3)	130 (7.3)¶	53 (3.9)	46 (2.6)**	22 (1.6)	204 (11.5)‡	185 (13.7)

NA, not available. \*Odds ratio 0.43 (95% CI 0.18; 0.52),  $P < 0.0001$ . †Odds ratio 0.55 (95% CI 0.41; 0.72),  $P < 0.0001$ . ¶ $P = 0.41$ . \*\*Odds ratio 0.43 (95% CI 0.34; 0.67),  $P < 0.0001$ . ‡Odds ratio 1.04 (95% CI 0.85; 1.26),  $P = 0.72$ ; however, with placebo, the odds ratio was 2.24 (1.76; 2.83),  $P < 0.0001$ , and the 95% CIs for verum and placebo studies did not overlap, indicating a significant difference ( $P < 0.05$ ) between short- and long-acting GLP-1 RAs relative to placebo.



sensitivity analyses. However, our conclusions cannot be generalized beyond the inclusion/exclusion criteria of the meta-analyzed trials.

In conclusion, the results of our meta-analysis indicate that long-acting GLP-1 RAs should preferentially be combined with basal insulin, since this combination results in not only better overall glycemic control (HbA<sub>1c</sub>) but also improved fasting plasma glucose concentrations and lower body weight. This combination also has advantages regarding gastrointestinal adverse events.

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