A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients

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ABSTRACT

Aims: To study differences in clinical outcomes between initiating glucagon-like peptide-1 receptor agonist (GLP-1 RAs) vs. insulin treatment in patients with type 2 diabetes treated with oral glucose-lowering medications (OGLM).

Methods: Prospective, randomized trials comparing GLP-1 RA and insulin treatment head-to-head as add-on to OGLM were identified (PubMed). Differences from baseline values were compared for HbA_{1c}, fasting plasma glucose, body weight, blood pressure, heart rate and lipoproteins. Proportions of patients reporting hypoglycaemic episodes were compared.

Results: Of 712 publications identified, 23 describing 19 clinical trials were included in the meta-analysis. Compared to insulin, GLP-1 RAs reduced HbA_{1c} more effectively (Δ - 0.17 %, $p < 0.0001$). Basal insulin was more effective in reducing fasting plasma glucose (Δ - 1.78 mmol/l, $p < 0.0001$). GLP-1 RAs reduced body weight more effectively (Δ - 3.71 kg; $p < 0.0001$). The proportion of patients experiencing hypoglycaemic episodes was 34 % lower with GLP-1 RAs ($p < 0.0001$), with a similar trend for severe hypoglycaemia. Systolic blood pressure was lower, the heart rate higher with GLP-1 RAs ($p < 0.0001$). Triglycerides and LDL cholesterol were significantly lower with GLP-1 RAs. Long-acting GLP-1 RAs were better than short-acting ones in reducing HbA_{1c} and fasting glucose, but similar regarding body weight.

Conclusions: Slightly better glycaemic control can be achieved by adding GLP-1 RAs to OGLM as compared to insulin treatment, with added benefits regarding body weight, hypoglycaemia, blood pressure and lipoproteins. These differences are in contrast to insulin being prescribed far more often than GLP-1 RAs.

Key Words:

GLP-1 receptor agonists, basal insulin, incretin-based glucose-lowering medications, short-acting GLP-1 receptor agonists, long-acting GLP-1 receptor agonists, type 2 diabetes, meta-analysis, body weight, lipoproteins

Introduction

Today, there are numerous options for treatment intensification in patients with type 2 diabetes, in whom monotherapy with metformin or combination therapy with oral glucose-lowering medications have failed [1-5]. If oral glucose-lowering medications have not been able to reach or maintain individual treatment goals, the initiation of injectable therapy has to be considered [1-5]. While insulin (often a "bedtime" therapy with long-acting insulin [6-11]) has long been the only option in this situation, the availability of GLP-1 RAs [12, 13] has introduced a second class of injectable glucose-lowering agents as an alternative to insulin treatment. Based on their mechanism of action, GLP-1 RAs, in addition to lowering plasma glucose and HbA_{1c}, also reduce body weight by decreasing appetite and caloric intake [12, 13]. Due to their glucose-dependent effects on insulin and glucagon secretion [14, 15], they do not provoke episodes of hypoglycaemia [12, 13].

In the past years, several meta-analyses have been carried out to compare the ability of GLP-1 RAs and insulin to improve glycaemic control and to influence cardiovascular risk factors such as body weight, blood pressure and lipoprotein profiles [16-20]. However, since their publication, novel compounds like lixisenatide, albiglutide, and dulaglutide have been introduced, which have not consistently been part of these previous analyses [16-20]. In addition, recent findings point to differences in the mode of action of short-acting GLP-1 RAs injected once or twice daily (exenatide b.i.d. [21] and lixisenatide [22], characterized by a typical intermittent exposure to active drug concentrations with their approved injection schedules) and long-acting GLP-1 RAs, injected once daily or once weekly (liraglutide [23], exenatide once weekly [24], dulaglutide [25], albiglutide [26], characterized by relatively constant elevations in drug concentrations without intermittent troughs). While long-acting GLP-1 RAs reduce fasting plasma glucose more, due to overnight exposure to significant drug concentrations, short-acting GLP-1 RAs have greater effects on preventing post-meal glycaemic excursions, because they maintain their ability to slow gastric emptying with long-term treatment, which typically is lost due to tachyphylaxis in the case of long-acting GLP-1 RAs [27-29]. Given the number of novel compounds in the class of GLP-1 RAs and

publications on their clinical effectiveness from head-to-head comparisons versus insulin treatment (Table 1), as well as an opportunity to explore differences between short-acting and long-acting GLP-1 RAs, we performed an updated meta-analysis. A special focus was on potential differences with respect to glycaemic control, body weight, blood pressure, heart rate and blood lipoprotein concentrations as well as the risk for hypoglycaemia. Furthermore, we added an analysis comparing the effects of GLP-1 RAs versus rapid-acting insulin on a background of basal insulin and oral glucose-lowering medications. Preliminary results have been presented in abstract form [30].

Materials and methods

The present meta-analysis was conducted according to the Preferred reporting items for systematic reviews and meta-analyses recommendations (PRISMA statement) [31].

Search strategy and inclusion criteria. A systematic PubMed search was conducted, using the search terms “GLP-1 receptor agonist”, “insulin”, “insulin glargine”, “insulin detemir”, “insulin aspart”, “insulin lispro”, “exenatide”, “liraglutide”, “lixisenatide”, “albiglutide”, “dulaglutide” and “taspoglutide”. In addition, the reference lists of the studies retrieved (including previous meta-analyses and review articles) were searched for additional citations. Included studies had to be randomized, prospective clinical trials with a head-to-head comparison of (a) a GLP-1 RA versus long-acting or pre-mixed insulin in type 2 diabetic patients on a background treatment of oral glucose-lowering medications or (b) of a GLP-1 RA versus rapid-acting insulin on a background treatment of basal insulin with or without concomitant oral glucose-lowering medications. Further inclusion criteria were a minimum duration of 12 weeks, 25 or more patients per treatment arm and a report of adverse events. Publications retrieved by this search strategy were screened (title and abstract) for eligibility by MAEA and MAN. In case of conflicting opinions, a third author was to finally decide (JJM). A total of 712 publications were identified, of which 19 studies (23 publications [32-54]) were found eligible for the present meta-analysis (Table 1, supplementary Figure 1). 16 studies compared GLP-1 RAs and basal insulin (13 studies) or premixed insulin (3 studies), on a background treatment with OGLM, while 3 studies reported a comparison of GLP-1 RAs and rapid-acting insulin, on a background treatment of basal insulin in combination with OGLM. The quality of publications eligible for the present analysis was judged by MAEA according to the Jadad score [55] (supplementary Table 1).

Data extraction. For all studies, study duration, background glucose-lowering medication, patient numbers and the proportion discontinuing the studies prematurely were recorded for each study arm. The patient-years of exposure and observation were calculated as the number of completers times study duration (in years) plus the number of patients withdrawing from the study times half of the study duration. The following variables were

extracted by treatment with either GLP-1 RAs or insulin as change between baseline values and those at study end: Glycated haemoglobin (HbA_{1c}), fasting plasma glucose, body weight, systolic and diastolic blood pressure, heart rate, triacylglycerol concentrations, LDL and HDL cholesterol. Numbers of patients reporting ≥ 1 episode of any hypoglycaemia, nocturnal hypoglycaemia, or severe hypoglycaemia (defined by a requirement for third-party assistance), and total numbers of patients examined in each study arm were recorded. For all study arms, the proportion of patients treated with sulfonylureas at baseline was recorded. In addition, events of acute myocardial infarction, stroke, and death reported as adverse events were recorded (for details, see online supplementary material, page 6).

Endpoints. The primary endpoint was the difference in HbA_{1c} reduction between baseline value and study end comparing GLP-1 RA and insulin treatment (Δ). Secondary endpoints were the mean change from baseline in fasting plasma glucose, body weight, blood pressure, heart rate, serum lipid and lipoprotein concentrations and the proportion of patients experiencing episodes of hypoglycaemia. The latter was also related to the proportion of patients treated with sulfonylureas as reported for the various study arms, by linear regression analysis (GraphPad Prism version 6.07 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com).

Meta-analysis. The present meta-analysis was performed employing Comprehensive Metaanalysis 2.2.064 (Biostat Inc., Inglewood, NJ, USA), imputing the sample size for each group (GLP-1 RA or insulin treatment), the mean changes from baseline and their standard deviations. Standard deviations were often not available from the original publications, but could be calculated from standard errors of the mean and sample size, 95 % confidence intervals of estimated treatment differences, or from their reported interquartile ranges. For head-to-head comparison versus insulin treatment, we defined subgroups of short- and long-acting GLP-1 RAs, and performed a meta-analysis by subgroup as well as an overall analysis comparing all GLP-1 RAs versus insulin treatment. The results of the meta-analysis (random-effects model) are reported as weighted differences in means (± 95 % confidence intervals), as well as Z- and p-values. For all analyses, a test of heterogeneity was

performed. Resulting Q-values as well as related p-values and I^2 are presented in the legends to figures displaying Forest plots designed with GraphPad Prism version 6.07.

Hypoglycaemic episodes. In the 19 studies included in the present analysis, any hypoglycaemia was defined by typical signs or symptoms, with or without confirmed low blood glucose levels (definitions ranging from < 3.0 to < 4.0 mmol/l in the different trials, Table 1). Severe hypoglycaemia was defined as an episode that required assistance of another person, with additional variations ranging from loss of consciousness, seizure or coma, to recovery after administration of oral carbohydrate, glucagon or glucose. Definitions for blood glucose limits were ranging from < 2.0 to < 3.1 mmol/l.

For the comparison of the proportion of patients experiencing hypoglycaemic episodes with GLP-1 RA vs. insulin treatment, we calculated the proportion of patients having experienced at least one hypoglycaemic episode (any, nocturnal, or severe, i.e. requiring third-party assistance) during all trials relative to the total number of participants, also addressing the subgroups of short- and long-acting GLP-1 RAs (only with a background medication of OGLM). Data on nocturnal hypoglycaemic episodes were only available from a single study on a background of basal insulin/OGLM [39]. We then calculated the difference (in percent) for all patients treated with insulin versus those treated with GLP-1 RAs, with related 95 % confidence intervals and p-values (MedCalc Statistical Software Version 15.2, MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2015). As a sensitivity analysis, the proportion of patients reporting hypoglycaemic episodes were also compared by meta-analysis, expressed as a rate ratio.

For the meta-regression analysis (Comprehensive Metaanalysis 2.2.064) of the proportion of patients with hypoglycaemic episodes under treatment with GLP-1 RAs or insulin therapy, we imputed the number of patients with hypoglycaemic episodes and the total number of patients in each treatment arm, with the percentage of patients with sulfonylureas as a concomitant medication as the moderator variable (calculated as the mean of the percentage from both the GLP-1 RA and the insulin arm).

Results

A total of 8854 patients had participated in the 19 studies analysed in the present meta-analysis (supplementary Figure 1). For the analysis of patients on a background medication with OGLM, a total of 7484 participants took part in the individual trials (representing 5648.6 patient-years of observation). 3976 patients had been randomized to GLP-1 RA, 3508 to insulin treatment (2937.3 versus 2711.4 patient-years of observation, respectively). 7 of the clinical trials with a head-to-head comparison of GLP-1 RA and insulin therapy reported on short-acting GLP-1 RAs (all exenatide b.i.d), while the remaining 9 trials reported on all approved long-acting GLP-1 RAs (Table 1).

The trials analysing GLP-1 RAs versus rapid-acting insulin on a background medication of basal insulin and OGLM comprised 1370 patients (representing 687.5 patient-years of observation). 688 participants were randomized to the GLP-1 RA, 682 to the insulin treatment arm (343.5 versus 344.0 patient-years of observation, respectively).

Table 1 shows the baseline characteristics of the participants for each study. One study [38] included only patients who had at least one cardiovascular risk factor; two studies [32, 45] comprised only Japanese patients.

Comparison of short-acting and long-acting GLP-1 RAs with insulin treatment

Glycaemic control. Short-acting GLP-1 receptor agonists had a similar effect on HbA_{1c} concentrations compared to insulin treatment (Δ - 0.02 % [95 % CI - 0.09 to 0.06, p = 0.70]), while long-acting GLP-1 RAs caused a significantly greater reduction than insulin treatment (Δ - 0.17 % [95 % CI - 0.22 to – 0.12, p < 0.0001]) (Figure 1). All GLP-1 RAs taken together caused a reduction greater than that with insulin treatment by Δ -0.12 % (95 % CI - 0.16 to – 0.07, p < 0.0001). This difference was driven by studies using long-acting GLP-1 RAs, while those using short-acting RAs showed no significant difference. Of note, there was substantial heterogeneity, with the results from Bergenstal et al. [34] event pointing to a better glycaemic control with insulin.

Basal insulin was superior to GLP-1 RAs in lowering fasting plasma glucose (Figure 2). The difference between short-acting GLP-1 RAs and insulin treatment was greater than that comparing long-acting compounds and insulin treatment (Δ 2.0 mmol/l [95 % CI 1.9 to 2.0, p < 0.0001] and Δ 0.8 [95 % CI 0.7 to 0.9, p < 0.0001], respectively). All GLP-1 RAs versus insulin treatment resulted in a difference of Δ 1.8 mmol/l (95 % CI 1.7 to 1.8, p < 0.0001).

Body weight. GLP-1 RA treatment was associated with weight loss, while insulin treatment led to weight gain in the studies analysed in the present meta-analysis (details not shown). Short-acting GLP-1 RAs achieved a greater difference versus insulin treatment in body weight (Δ - 5.1 kg [95 % CI - 5.4 to - 4.8, p < 0.0001]) than did long-acting compounds (Δ - 3.3 kg [95 % CI – 3.5 to – 3.1, p < 0.0001]) (Figure 3). The body weight reduction for all GLP-1 RAs compared to insulin treatment amounted to Δ – 3.7 kg (95 % CI - 3.9 to – 3.5, p < 0.0001).

Blood pressure. Systolic blood pressure was lowered with GLP-1 RA treatment, but remained more or less unchanged with insulin therapy (details not shown). Short-acting compounds led to a greater reduction versus insulin therapy than long-acting GLP-1 RAs (Δ - 5.0 mmHg [95 % CI – 7.1 to – 2.9, p < 0.0001] and Δ - 2.4 mmHg [95 % CI – 3.3 to –1.6, p < 0.0001], respectively) (supplementary Figure 2). The difference of all GLP-1 RAs compared to insulin treatment amounted to Δ - 2.8 mmHg (95 % CI – 3.6 to – 2.0, p < 0.0001). A similar tendency was found for diastolic blood pressure (details not shown).

Heart rate. GLP-1 RA treatment was associated with an increase in heart rate, while insulin therapy tended to lower heart rate (details not shown). The difference of long-acting GLP-1 RAs compared to insulin treatment amounted to Δ 2.6 bpm (95 % CI 2.1 to 3.2, p < 0.0001) (supplementary Figure 2). None of the studies with short-acting GLP-1 RAs reported heart rate changes, which might reflect on the fact that the circulating plasma levels of these compounds were likely very low at the time of heart rate assessment, if the drugs had last been administered on the preceding day.

Serum lipid and lipoprotein concentrations. Short-acting GLP-1 RAs compared to insulin therapy resulted in a difference in triacylglycerol concentrations of Δ 0.03 mmol/l (95 % CI –

0.19 to 0.25, p = 0.79). Long-acting compounds versus insulin treatment led to a relative reduction of Δ - 0.26 mmol/l (95 % CI - 0.34 to – 0.19, p < 0.0001). The difference in triacylglycerol concentrations between all GLP-1 RA and insulin therapy amounted to Δ - 0.23 mmol/l (95 % CI – 0.31 to – 0.16, p < 0.0001) (supplementary Figure 3).
LDL cholesterol concentrations were reduced vs. baseline with GLP-1 RAs, and remained more or less unchanged with insulin treatement (details not shown), with a difference of Δ - 0.13 mmol/l (95 % CI – 0.28 to 0.02, p = 0.080) for short-acting GLP-1 RAs, of Δ - 0.13 mmol/l (95 % CI – 0.18 to – 0.09, p < 0.0001) for long-acting compounds, and of Δ - 0.13 mmol/l (95 % CI – 0.18 to – 0.09, p < 0.0001) for all GLP-1 RAs compared to insulin treatment (supplementary Figure 3).

There were no significant differences regarding HDL cholesterol (details not shown).

Hypoglycaemia. When comparing GLP-1 RA to insulin treatment, on a background therapy of OGLM, we found a significant reduction in the proportion of patients experiencing any hypoglycaemia or nocturnal hypoglycaemia by approximately 35-45 % (Table 2). A similar result was found regarding severe hypoglycaemia with short-acting GLP-1 RAs. However, with long-acting GLP-1 RAs, a reverse trend was found, basically as a consequence of a single study reporting several patients experiencing severe hypoglycaemic episodes with liraglutide, but none with insulin *glargine* treatment [49]. A sensitivity analysis using meta-analysis for comparing hypoglycaemia between GLP-1 RA and insulin treatment resulted in similar reductions in the proportion of patients experiencing different categories of hypoglycaemic episodes.

In patients receiving treatment with GLP-1 RAs, the sulfonylurea-use was positively correlated with the proportion of patients experiencing any hypoglycaemic episodes (supplementary Figure 4). A similar trend was observed in patients treated with insulin, however, with a higher risk for hypoglycaemia already when no or few patients were treated with sulfonylureas (supplementary Figure 4).

Comparison of GLP-1 RAs with rapid-acting insulin on a basal insulin/oral glucose-lowering medication background.

GLP-1 RAs had a similar effect on HbA_{1c} values as treatment with rapid-acting insulin, with a difference (Δ) of 0.02 % (95 % CI – 0.08 to 0.11, p = 0.73) (Figure 1 B). GLP-1 RAs were significantly more effective than rapid-acting insulin in lowering fasting plasma glucose (Δ -0.75 mmol/l [95 % CI – 0.87 to – 0.64, p < 0.0001]) (Figure 2 B). Compared to rapid-acting insulin, GLP-1 RAs had a favourable influence on body weight, with a reduction of Δ – 1.3 kg compared to baseline (95 % CI - 1.5 to - 1.1, p < 0.0001) (Figure 3 B). For short-acting GLP-1 RAs compared to rapid-acting insulin on a background of basal insulin and OGLM, a reduction was found for any hypoglycaemia (by 35 %) and severe hypoglycaemia (by 77 %, not significant), while the risk for nocturnal hypoglycaemia was similar.

Discussion

The results of the present meta-analysis indicate that GLP-1 RAs have a similar impact on the reduction of HbA_{1c} values, when compared to treatment with simple insulin regimens like "bedtime" basal insulin once daily or twice daily premixed insulin (Figure 1). If anything, overall glycaemic control was slightly better with GLP-1 RAs than with insulin treatment (Figure 1). This was more obvious, in studies using long-acting GLP-1 RAs, while short-acting GLP-1 RAs lead to glycaemic control similar to insulin treatment. The better glycaemic control with (particularly long-acting) GLP-1 RAs was the case, although fasting plasma glucose was better controlled by insulin (Figure 2), especially in comparison to short-acting GLP-1 RAs. This may be considered expected, since especially basal insulin mainly addresses the control of fasting glucose concentrations [7, 8, 56]. The difference in fasting glucose concentrations was more pronounced when short-acting GLP-1 RAs were compared to insulin treatment. The likely reason is the low exposure to effective drug levels overnight with short-acting GLP-1 RAs [21, 22]. Nevertheless, even compared to long-acting GLP-1 RAs, insulin was superior in controlling fasting glycaemia (Figure 2). The apparent discrepancy between differences in HbA_{1c} control (better with GLP-1 RA) and the control of fasting plasma glucose (better with insulin regimens) implies a more effective prevention of post-prandial glycaemic excursions with GLP-1 RAs, in line with mechanistic studies showing a reduction in meal-related glucose increments with GLP-1 RAs [57, 58]. The main mechanisms are a stimulation of insulin and a suppression of glucagon secretion as well as a deceleration in gastric emptying [27, 57]. The balance between these mechanisms may vary with the degree of tachyphylaxis for slowing gastric emptying, which is especially typical for long-acting GLP-1 RAs [24, 29]. The obvious heterogeneity between the studies analysed, with Bergenstal et al.'s results even pointing to better glycaemic results with insulin treatment, may be due to the fact that there was an exceptionally high baseline HbA_{1c} (10 2 % vs. 7.5-9.1 % in the other studies), and that premixed insulin was used [34].

Furthermore, the present meta-analysis of published head-to-head comparisons between GLP-1 RA and insulin treatment confirms a relatively favourable influence of GLP-1 RAs on

body weight, systolic blood pressure, and triacylglycerol concentrations, as well as the proportion of patients experiencing episodes of hypoglycaemia [16-20, 59]. In our analysis, short-acting GLP-1 RAs were associated with greater reductions in body weight and both systolic and diastolic blood pressure, while long-acting GLP-1 RAs had a relatively greater influence on HbA_{1c}, triacylglycerol and LDL cholesterol concentrations. This difference in the influence of GLP-1 RA treatment on body weight is at variance with reports of head-to-head comparisons of short- and long-acting GLP-1 RAs, which have typically found no difference in the weight-reducing effects [24, 60]. The apparent difference is probably due to the fact that we performed an indirect comparison.

The influence of GLP-1 RA vs. insulin treatment on body weight [61, 62], systolic blood pressure [63], heart rate [63] and hypoglycaemia we describe confirm previous findings [16-20]. Since, especially with short-acting GLP-1 RAs, there may be a diurnal variation in blood pressure and heart rate [57], the time point of measuring these parameters may become important for detecting differences. Unfortunately, most publications did not report details in that respect. Regarding hypoglycaemia, episodes appear to mainly be confined to patients who have sulfonylureas as part of their background glucose-lowering medication (supplementary Figure 4). However, our results indicate that the risk for hypoglycaemia is greater when sulfonylureas are combined with basal insulin rather than GLP-1 RAs, in line with previous findings from individual studies [40].

Another finding of our present analysis is a small, but robust reduction in LDL cholesterol with GLP-1 RAs, but not with insulin therapy, resulting in a statistically significant difference in favour of GLP-1 RAs (supplementary Figure 3). Based on two [18] and 7 studies [19] analysed, respectively, similar findings have been indicated versus insulin *glargine*. We now confirm this based on data from 8 studies, all comparing GLP-1 RAs with insulin.

A recent meta-analysis of 31 studies (including 4 studies comparing GLP-1 RAs to placebo and/or glimepiride), has compared the influence of GLP-1, GLP-1 RAs and DPP-4 inhibitors to various other glucose-lowering agents [59]. This meta-analysis also reported significantly greater reductions in total and LDL cholesterol as well as triglycerides. The

mechanism for the reduction in LDL cholesterol is not entirely clear, but may be partially related to the weight difference (Figure 3), since intensive lifestyle programs aiming at weight reduction are accompanied by a small, but significant reduction in LDL cholesterol [64].

The direct comparison of GLP-1 RAs and rapid-acting insulin, on a background of basal insulin and OGLM, showed a significantly greater reduction in fasting plasma glucose (Figure 2 B), body weight (Figure 3 B) and in the proportion of patients with any or severe hypoglycaemic episodes (Table 2) under treatment with GLP-1 RAs, while we could not detect a difference in the reduction of HbA_{1c} values (Figure 1 B). Nocturnal hypoglycaemia was not significantly different. This may be expected, since both treatment regimens compared expose patients to basal insulin overnight, while short-acting GLP-1 RAs and rapid acting insulin are timed with meals and their actions should not extend into the nocturnal period.

Since only one study [39] included data for the change from baseline in heart rate, blood pressure and serum lipids/lipoproteins, no meta-analysis was carried out for these parameters.

Favourable effects on cardiovascular risk factors/markers like body weight, systolic blood pressure, triglycerides, LDL cholesterol for GLP-1 RAs may translate into a favourable cardiovascular risk overall. Obviously, these parameters are not influenced by insulin treatment as favourably. It is an open question whether initiating GLP-1 RA or insulin treatment will have a differential effect on cardiovascular risk and/or event rates. The recent LEADER study reported reduced cardiovascular event rates with liraglutide as compared to placebo treatment, both in combination with standard care [65], suggesting some long-term benefit from the changes in risk factors also described in the present study. However, our comparison appears to have its own merit, since typically, in patients failing glycaemic control with oral glucose-lowering medications, the choice for treatment intensification is either GLP-1 RA or insulin treatment. It may be of interest to initiate prospective trials comparing these treatments, and our analysis may be taken as providing a rationale for this suggestion. A recent publication by Anyanwagu et al. [66] has also shown a lower incidence

of cardiovascular events after treatment intensification with GLP-1 RAs as compared to insulin in a retrospective study of patients with type 2 diabetes. A preliminary look at cardiovascular events reported as adverse events in the studies contributing to the present analysis indicated too few events for a meaningful comparison, based on the lack of power to even detect major differences in event rates (see online supplementary material, page 6).

Of note, there is considerable heterogeneity between studies. In populations of Asian origin [32, 45], GLP-1 RA may be of particular effectiveness due to pathophysiological peculiarities of Asian type 2 diabetes and due to differences in body size and degree of obesity. Differences in baseline HbA_{1c} probably do not explain much of the heterogeneity, since Buse et al. 2015 found no difference in the HbA_{1c}-lowering capacity between GLP-1 RAs and insulin regimens when analyzed by categories of baseline HbA_{1c}. Furthermore, obvious differences between effects of short- and long-acting GLP-1 RAs probably contribute to overall heterogeneity.

There were several limitations to the present meta-analysis. None of the included trials was double-blinded. All head-to-head-comparisons of GLP-1 RA and insulin treatment were open-label studies, which might have led to some bias. The quality of reporting was not perfect based on the Jadad score [55], as summarized in supplementary Table 1. The study duration (Table 1) was short relative to the many years that both treatments may be carried out in type 2-diabetic patients. The analysis of cardiovascular events was hampered by their low number as reported in the contributing publications.

In conclusion, GLP-1 RAs, as compared to insulin treatment, show a beneficial effect on the cardiovascular risk profiles. Furthermore GLP-1 RAs, though being injectable compounds, can be administered based on easier regimens, with standard doses rather than individual titration, an injection frequency ranging from twice daily (exenatide b.i.d.) to once weekly (exenatide q.w., dulaglutide, albiglutide), as compared to one (long-acting basal insulin) or two (premixed insulin) injections per day. The study centers participating in the studies analysed in the present meta-analysis can be assumed to be highly skilled in complex diabetes treatment regimens. This could mean that, compared to the trial results

used for the present analysis, in the “real world” the easier-to-implement regimens with GLP-1 RAs may offer further advantages over insulin regimens. Our results are in contrast to the fact that, in clinical practice, insulin is still used far more often than GLP-1 RAs for the treatment of type 2 diabetes. This may be a consequence of higher rates of “gastrointestinal” adverse events and withdrawal rates with GLP-1 RAs (supplementary Table 2). Additionally, depending on the health care system, there may be differences in costs in favour of insulin treatment. In addition, fear of serious adverse events like acute pancreatitis and pancreatic or thyroid cancer [67] may have prevented a more readily uptake of GLP-1 RAs. Since recent data indicate smaller risks in this respect than previously reported [68, 69], and since the overall experience with GLP-1 RAs has grown, there may no longer be as much of a reason to hesitate using GLP-1 RAs.

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Declaration of interests

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Contributor statements

MAEA, MK, JJM and MAN designed the meta-analysis. MAEA, MAN and JJM screened publications for eligibility. The quality of publications was judged by MAEA. MAEA, MK and MAN analysed the data and performed the statistical analysis. Figures were designed by MK and MAEA. MAEA and MAN wrote the manuscript. All authors reviewed/edited the manuscript, approved the final draft and decided to submit it for publication.

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Table 1. Baseline characteristics of patients and study protocol details (duration, treatment, background medication) for the studies analysed in the present meta-analysis

Study	Study duration [weeks]	Study medication	Comparator	Background treatment (at randomization)	% of patients treated with sulfonyl-ureas (SU)	Sample size GLP-1 RA/ Insulin (n)	Proportion of the study population being male [%]	Mean duration of diabetes [years]	Mean age [years]	Mean BMI [kg/m^2]	Mean baseline HbA_{1c} [%]
GLP-1 receptor agonists (GLP-1 RAs) vs. basal insulin (+ oral glucose-lowering medication)											
Short-acting GLP-1 RAs											
Heine et al. 2005 [44]	26	Exenatide b.i.d.[a]	Insulin *glargine*	Met[b] + SU	100	282/267	55.8	9.6	58.9	31.4	8.3
Barnett et al. 2007 [33]	16	Exenatide b.i.d.	Insulin *glargine*	Met or SU	44.9	68/70	47.1	7.5	54.9	31.1	8.9
Nauck et al. 2007 [47]	52	Exenatide b.i.d.	BIA[c] 70/30 b.i.d.	Met + SU	100	253/248	51.0	9.9	58.5	30.4	8.6
Bergenstal et al. 2009 [34]	24	Exenatide b.i.d.	BIA 70/30 q.d. or b.i.d.	Met + SU	100	124/124/ 124[d]	48.1	9.0	52.4	33.8	10.2
Bunck et al. 2009 [35]	52	Exenatide b.i.d.	Insulin *glargine*	Met	0	36/33	65.3	4.9	58.4	30.5	7.5
Davies et al. 2009 [38]	26	Exenatide b.i.d.	Insulin *glargine*	Met/SU/TZD[e]	85.3	118/117	68.4	8.7	56.5	34.2	8.6
Gallwitz et al. 2011 [41]	26	Exenatide b.i.d.	BIA 70/30 q.d.	Met	0	181/173	-[g]	5.0	57.0	33.2	7.9
Long-acting GLP-1 RAs											
Diamant et al. 2010 [40]	26	Exenatide q.w.[f]	Insulin *glargine*	Met ± SU	30.0	233/223	53.3	7.9	58.0	32.0	8.3
Inagaki et al. 2012 [45]	26	Exenatide q.w.	Insulin *glargine*	BG[h] ± TZD	59.7	215/212	67.9	9.0	56.8	26.1	8.5
Davies et al. 2013 [37]	26	Exenatide q.w.	Insulin *glargine*	Met ± SU	-[g]	111/105	66.5	7.5	58.5	33.7	8.4
Weissman et al. 2014 [50]	52	Albiglutide q.w.	Insulin *glargine*	Met ± SU	81.8	504/241	55.8	8.7	55.3	33.1	8.3
Russell-Jones et al. 2009 [49]	26	Liraglutide q.w.	Insulin *glargine*	Met + SU	100	230/232	58.5	9.5	57.7	30.4	8.3
D'Alessio et al. 2015 [36]	24	Liraglutide q.w.	Insulin *glargine*	Met ± SU	68.3	481/484	54.4	8.5[i]	57.3	31.9	9.1
Gough et al. 2015 [43]	52	Liraglutide q.w.	Insulin *glargine*	Met ± TZD	0	414/413	49.3	7.1	55.0	31.3	8.3
Araki et al. 2015 [32]	26	Dulaglutide q.w.	Insulin *glargine*	BG[j] and/or SU	64.0	181/180	71.5	8.9	56.8	26.0	8.1
Giorgino et al. 2015 [42]	78	Dulaglutide q.w.	Insulin *glargine*	Met + SU	100	273/272/262[k]	51.3	9.0	56.7	31.7	8.1
GLP-1 RAs vs. rapid-acting insulin (+ basal insulin)											
Diamant et al. 2014 [39]	30	Exenatide b.i.d.	Insulin *lispro* t.i.d.	Met	0	315/312	32.4	11.5[g]	59.5	32.5	8.3
Mathieu et al. 2014 [46]	26	Liraglutide q.d.	Insulin *aspart* q.d.	Met	0	88/89	65.6	12.4	61.0	32.3	7.7
Rosenstock et al. 2014 [48]	26	Albiglutide q.d.	Insulin *lispro* t.i.d.	Met, TZD, SU, PIO[l], AGI[m]	5.3	285/281	47.0	11.0	55.6	-[g]	8.5

[a]: bis in die = twice a day, [b]: Metformin, [c]: BIA = Biphasic insulin *aspart*, [d]: numbers are given for the study arms exenatide b.i.d./BIA 70/30 q.d./BIA 70/30 b.i.d., [e]: Met+SU or Met+TZD (thiazolidinedione) or SU+TZD or Met+SU+TZD, [f]: q.w. = once weekly, [g]: no precise numbers given, [h]: biguanide derivate, [i]median, [j]: patients were receiving metformin or buformin, [k]: numbers are given for the study arms dulaglutide q.w. 1.5 mg/ dulaglutide q.w. 0.75 mg/insulin *glargine*, [l]: pioglitazone, [m]: α-glucosidase inhibitors

Table 2. Proportion of patients reporting any episode of hypoglycaemia, nocturnal episodes of hypoglycaemia, or severe hypoglycaemia in head-to-head trials comparing GLP-1 RAs and insulin therapy, both on a background of oral glucose-lowering medications and of basal insulin plus oral glucose-lowering agents.

Background glucose-lowering medication	Category of hypoglycaemia	Type of GLP-1 RA[a]	GLP-1 RA treatment [n with ≥ 1 hypoglycaemic episodes/n all patients (% with ≥ 1 hypoglycaemic episodes)]	Insulin treatment [n with ≥ 1 hypoglycaemic episodes/n all patients (% with ≥ 1 hypoglycaemic episodes)]	Absolute difference insulin – GLP-1 RA treatment (± 95 % confidence interval)	Significance (p-value)
Oral glucose-lowering medication	Any hypoglycaemia	Short-acting	122/527 (23.1)	275/641 (42.9)	19.8 (14.4–25.1)	< 0.0001
		Long-acting	710/2500 (28.4)	836/1939 (43.1)	14.7 (11.8–17.6)	< 0.0001
		All	832/3027 (27.5)	1111/2580 (43.1)	15.6 (13.1–18.1)	< 0.0001
	Nocturnal hypoglycaemia	Short-acting	65/552 (11.8)	109/538 (20.3)	8.4 (4.0-12.9)	0.0002
		Long-acting	167/1763 (9.5)	265/1475 (18.0)	8.5 (6.1-11.0)	< 0.0001
		All	232/2315 (10.0)	374/2013 (18.6)	8.6 (6.4-10.7)	< 0.0001
	Severe hypoglycaemia[b]	Short-acting	9/1062 (0.9)	23/1156 (2.0)	1.1 (0.9-2.2)	0.039
		Long-acting	12/2500 (0.5)	5/1939 (0.3)	-0.2 (-0.6-0.2)	0.35
		All	21/3562 (0.6)	28/3095 (0.9)	0.3 (-0.1-0.8)	0.18
Basal insulin + OGLM	Any hypoglycaemia	Short- and long-acting	156/688 (24.0)	254/682 (37.2)	13.2 (8.2-18.1)	< 0.0001
	Nocturnal hypoglycaemia	Short-acting[c]	79/315 (25.1)	84/312 (26.9)	1.8 (-5.3-8.9)	0.67
	Severe hypoglycaemia[b]	Short- and long-acting	2/688 (0.3)	9/682 (1.3)	1.0 (-0.0-2.2)	0.076

[a]: GLP-1RA: GLP-1 receptor agonist(s); [b]: A hypoglycaemic episode requiring third-party assistance; [c]: Data are available for a single study only [39].

Figures

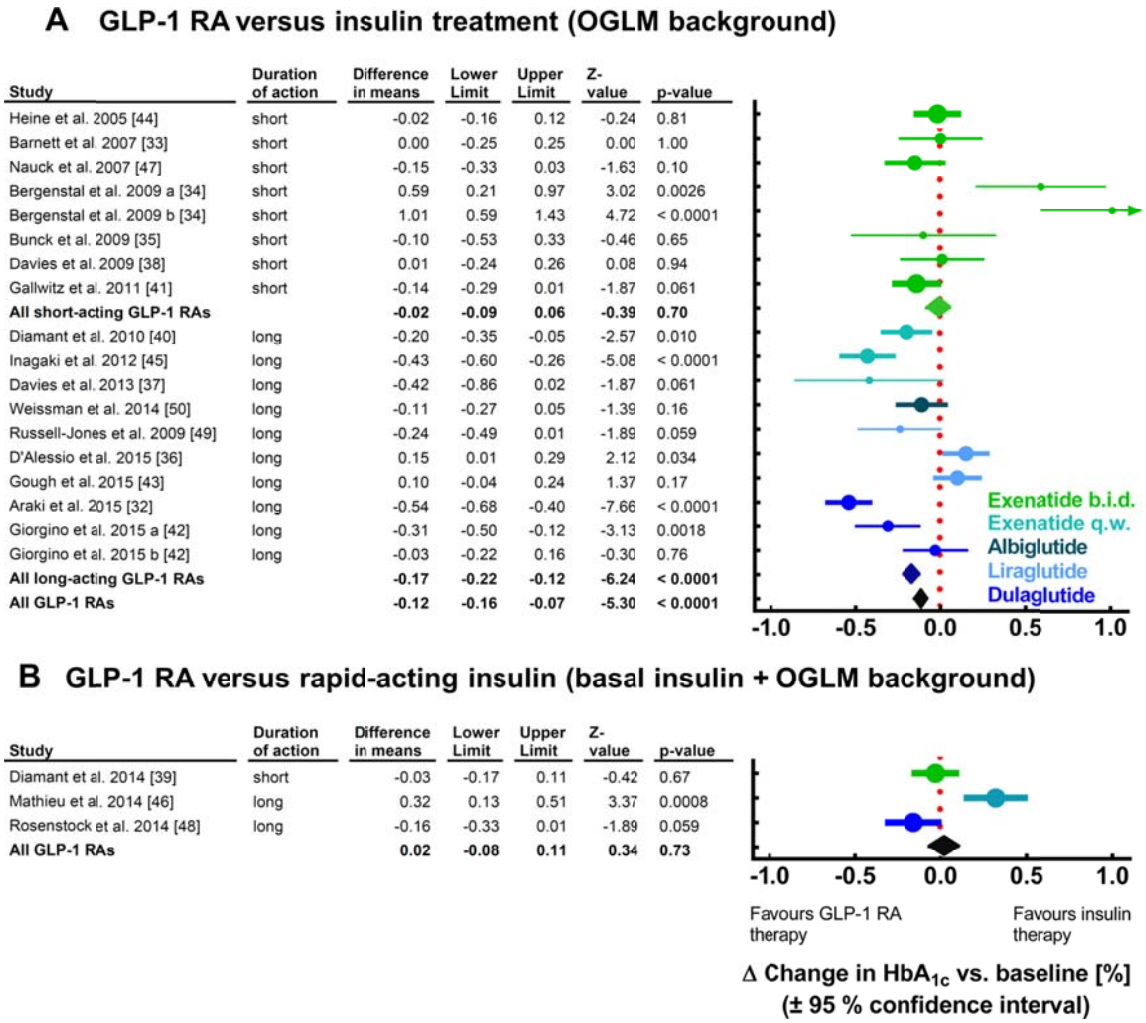
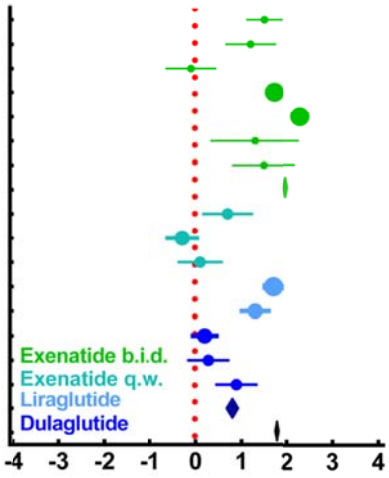


Fig. 1. Meta-analysis (Forest plot) depicting the difference between GLP-1 receptor agonist (GLP-1 RA) and insulin treatment regarding a change between baseline and study end in glycated haemoglobin. Panel A summarizes studies performed in patients on a background medication of oral glucose-lowering medications (OGLM), and also displays a subgroup analysis of patients treated with short- versus long-acting GLP-1 RAs. Panel B compiles studies in patients previously treated with basal insulin (+ oral glucose-lowering medications). Studies are referred to by the first authors' names and the year of publication. The Z- and p-values resulting for individual studies, subgroups, and the overall analysis are presented. Short-acting GLP-1 RAs are shown in green, and long-acting ones in blue, with individual colors for each compound (see legend; b.i.d. = twice daily, q.w. = once weekly). Diamonds show summary measures by subgroup or for the overall analysis. Filled circles and error bars indicate results for individual compounds and their 95 % confidence intervals. The size of the symbol represents the relative weight of the individual study for the subgroup analysis (0 - 5.0, 5.1 - 10, 10.1 – 20.0 or > 20 %, respectively). Heterogeneity (random effects analysis): A: $Q = 5.22$, $p = 0.022$. B: $Q = 15.0$, $p = 0.001$, $I^2 = 86.6$.

A GLP-1 RA versus insulin treatment (OGLM background)

Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Heine et al. 2005 [44]	short	1.20	0.65	1.75	7.36	< 0.0001
Barnett et al. 2007 [33]	short	1.72	1.64	1.80	4.25	< 0.0001
Nauck et al. 2007 [47]	short	2.29	2.21	2.37	-0.35	0.72
Bergenstal et al. 2009 a [34]	short	1.30	0.33	2.27	41.67	< 0.0001
Bergenstal et al. 2009 b [34]	short	1.49	0.80	2.18	55.47	< 0.0001
Bunck et al. 2009 [35]	short	1.50	1.10	1.90	2.63	0.0086
Davies et al. 2009 [38]	short	-0.10	-0.65	0.45	4.21	< 0.0001
All short-acting GLP-1 RAs		**1.96**	**1.90**	**2.02**	**68.88**	**< 0.0001**
Diamant et al. 2010 [40]	long	1.70	1.46	1.94	2.47	0.013
Inagaki et al. 2012 [45]	long	1.30	0.96	1.64	-1.54	0.12
Davies et al. 2013 [37]	long	0.10	-0.40	0.60	0.40	0.69
D'Alessio et al. 2015 [36]	long	0.70	0.15	1.26	13.73	< 0.0001
Gough et al. 2015 [43]	long	-0.29	-0.66	0.08	7.48	< 0.0001
Araki et al. 2015 [32]	long	0.28	-0.18	0.74	1.28	0.20
Giorgino et al. 2015 a [42]	long	0.89	0.43	1.35	1.19	0.23
Giorgino et al. 2015 b [42]	long	0.20	-0.11	0.51	3.77	0.0002
All long-acting GLP-1 RAs		**0.80**	**0.67**	**0.93**	**12.17**	**< 0.0001**
All GLP-1 RAs		**1.78**	**1.73**	**1.83**	**68.03**	**< 0.0001**



B GLP-1 RA versus rapid-acting insulin (basal insulin + OGLM background)

Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Diamant et al. 2014 [39]	short	-0.64	-0.93	-0.35	-4.25	< 0.0001
Mathieu et al. 2014 [46]	long	0.06	-0.65	0.77	0.17	0.87
Rosenstock et al. 2014 [48]	long	-0.28	-0.31	-0.25	-17.39	< 0.0001
All GLP-1 RAs		**-0.28**	**-0.31**	**-0.26**	**-13.15**	**< 0.0001**

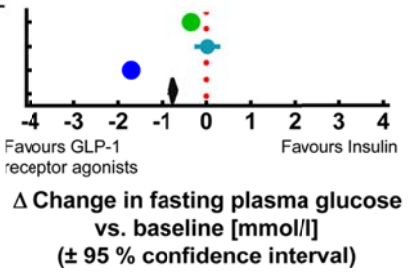
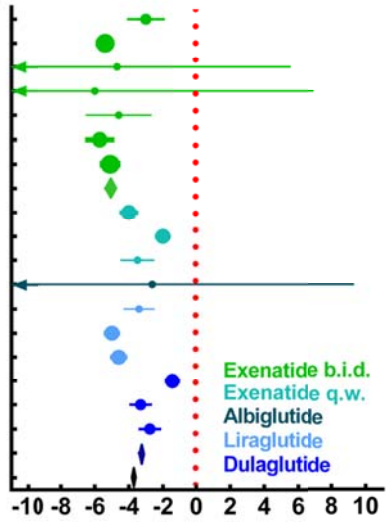


Fig. 2. Meta-analysis (Forest plot) depicting the difference between GLP-1 receptor agonist and insulin treatment regarding a change between baseline and study end in fasting plasma glucose. For details, see legend to Figure 1. Heterogeneity: A: Q = 5.88, p = 0.015. B: Q = 147.4, p < 0.001, I^2 = 98.6.

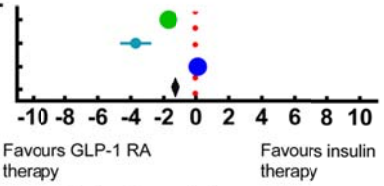
A GLP-1 RA versus insulin treatment (OGLM background)

Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Barnett et al. 2007 [33]	short	-3.00	-4.11	-1.89	-5.30	< 0.0001
Nauck et al. 2007 [47]	short	-5.40	-5.95	-4.85	-19.09	< 0.0001
Bergenstal et al. 2009 a [34]	short	-4.70	-14.96	5.56	-0.90	0.37
Bergenstal et al. 2009 b [34]	short	-6.00	-18.94	6.94	-0.91	0.36
Bunck et al. 2009 [35]	short	-4.60	-6.54	-2.66	-4.65	< 0.0001
Davies et al. 2009 [38]	short	-5.71	-6.57	-4.85	-13.03	< 0.0001
Gallwitz et al. 2011 [41]	short	-5.10	-5.71	-4.49	-16.39	< 0.0001
All short-acting GLP-1 RAs		**-5.10**	**-5.44**	**-4.75**	**-28.93**	**< 0.0001**
Diamant et al. 2010 [40]	long	-4.00	-4.56	-3.45	-14.13	< 0.0001
Inagaki et al. 2012 [45]	long	-2.01	-2.48	-1.54	-8.36	< 0.0001
Davies et al. 2013 [37]	long	-3.50	-4.50	-2.50	-6.85	< 0.0001
Weissman et al. 2014 [50]	long	-2.63	-14.58	9.32	-0.43	0.67
Russell-Jones et al. 2009 [49]	long	-3.40	-4.32	-2.49	-7.29	< 0.0001
D'Alessio et al. 2015 [36]	long	-5.00	-5.48	-4.52	-20.41	< 0.0001
Gough et al. 2015 [43]	long	-4.60	-5.11	-4.09	-17.60	< 0.0001
Araki et al. 2015 [32]	long	-1.42	-1.89	-0.95	-5.90	< 0.0001
Giorgino et al. 2015 a [42]	long	-3.31	-3.98	-2.64	-9.75	< 0.0001
Giorgino et al. 2015 b [42]	long	-2.77	-3.44	-2.11	-8.16	< 0.0001
All long-acting GLP-1 RAs		**-3.28**	**-3.47**	**-3.09**	**-33.48**	**< 0.0001**
All GLP-1 RAs		**-3.71**	**-3.88**	**-3.54**	**-43.32**	**< 0.0001**



B GLP-1 RA versus rapid-acting insulin (basal insulin + OGLM background)

Study	Duration of action	Difference in means	Lower Limit	Upper Limit	Z-value	p-value
Diamant et al. 2014 [39]	short	-1.70	-1.98	-1.42	-12.02	< 0.0001
Mathieu et al. 2014 [46]	long	3.70	-4.65	-2.75	-7.66	< 0.0001
Rosenstock et al. 2014 [48]	long	0.12	-0.29	0.53	0.57	0.57
All GLP-1 RAs		**-1.28**	**-1.50**	**-1.05**	**-11.19**	**< 0.0001**



Δ Change in body weight vs. baseline [kg] (± 95 % confidence interval)

Fig. 3. Meta-analysis (Forest plot) depicting the difference between GLP-1 receptor agonist and insulin treatment regarding a change between baseline and study end in body weight. For details, see legend to Figure 1. Heterogeneity: A: Q = 4.14, p = 0.042. B: Q = 78.3, p < 0.001, I^2 = 97.4.