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CLINICAL STUDY

Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials

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Abstract

Objective: The role of glucagon-like peptide-1 (GLP-1) receptor agonists in the treatment of type 2 diabetes is debated; many recent trials, which were not included in previous meta-analyses, could add relevant information.

Design and methods: All available randomized controlled trials (RCTs), either published or unpublished, performed in type 2 diabetic patients with GLP-1 receptor agonists (exenatide and liraglutide), with a duration >12 weeks were meta-analysed for HbA1c, body mass index, hypoglycaemia and other adverse events.

Results and conclusions: A total of 21 RCTs (six of which unpublished), enrolling 5429 and 3053 patients (with GLP-1 receptor agonists and active comparator or placebo respectively), was retrieved and included in the analysis. GLP-1 receptor agonists determine a significant improvement of HbA1c in comparison with placebo (-1.0 (-1.1, -0.8), $P<0.001$), with a low risk of hypoglycaemia. There is no evidence of increased cardiovascular risk with the use of GLP-1 receptor agonists. GLP-1 receptor agonists, which induce weight loss, are associated with gastrointestinal side effects. GLP-1 receptor agonists are effective in reducing HbA1c and postprandial glucose. In patients failing to sulphonylureas and/or metformin, GLP-1 receptor agonists are similarly effective as insulin. Available data suggest that the efficacy and tolerability of the novel agent, liraglutide, which is adequate for once-a-day administration, are comparable with those of exenatide bis in die.

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Introduction

The glucagon-like peptide-1 (GLP-1) receptor agonist exenatide has recently been introduced in the treatment of type 2 diabetic patients inadequately controlled with metformin and/or sulphonylureas (1, 2). Other drugs of the same class, such as liraglutide (3), are presently under development, and will soon be available in many countries.

The role of those new drugs in the treatment of type 2 diabetes is debated. The Consensus algorithm of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (4) suggests to limit the use of GLP-1 receptor agonists only to some specific cases, without considering those agents in the mainstream of the algorithm. The reasons for this exclusion are their perceived limited efficacy on HbA1c in comparison with other agents, their poorly defined safety profile, and their cost (4).

Efficacy and safety need to be assessed through a comprehensive revision of presently available clinical trials. Some detailed reviews of published studies are available (5, 6); furthermore, only one meta-analysis has been performed (7). However, presently available meta-analyses include only published studies, without any attempt at retrieving data from completed and publicly disclosed, although not formally published, clinical trials. Since very few studies on liraglutide have been published in extensive form to date (3, 8–10), presently available meta-analysis do not provide comprehensive information on the clinical profile of this agent.

The aim of the present study is to offer a comprehensive and updated synthesis of all available clinical data on safety and efficacy of GLP-1 receptor agonists.

Materials and methods

A meta-analysis was performed including all randomized clinical trials, either with a cross-over or a parallel series design, enrolling patients with type 2 diabetes, with a duration of at least 12 weeks, comparing GLP-1 receptor agonists with placebo or other active drugs. Trials with a shorter duration were excluded, due to the fact that they could not yield relevant information on

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HbA1c, which had been chosen as the principal outcome variable. The QUOROM checklist and flow diagram were used to present abstract, introduction, methods, results and discussion sections.

A Medline search for all articles in English, using the keywords 'exenatide' or 'liraglutide' was performed on November 25th, 2008. Randomized clinical trials were then selected. The identification of relevant abstracts, the selection of studies based on the criteria described above, and the subsequent data extraction were performed independently by two of the authors (E M, M M), and conflicts resolved by the third investigator (N M). The quality of trials was assessed using some items of the scale proposed by Jadad *et al.* (11). A further search was performed on EMBASE for randomized clinical trials on humans, in English, up to September 1st, 2008, using the keyword 'liraglutide' or 'exenatide', and on Cochrane database, on December 31st, 2008, with the same keywords and with no further limits.

Completed but still unpublished trials were identified through a search of www.clinicaltrials.gov website. Results of those trials were retrieved, if available, on www.novonordisk-trials.com or www.clinicalstudy-results.org; a manual search of abstracts from the last (2008) annual congresses of the ADA and of the EASD was performed, in order to retrieve information on results of unpublished trials (www.easd.org and http://professional.diabetes.org/CongressReports_List.aspx). For unpublished and published trials which were not exhaustively disclosed, an attempt was made (through e-mail) to contact principal investigators in order to retrieve missing data.

The principal outcome was the effect of GLP-1 receptor agonists, compared with other hypoglycaemic agents or placebo, on HbA1c at the end of the trial. Secondary outcomes included body mass index (BMI) at the end of the trial. Furthermore, data on the incidence of severe or any hypoglycaemia (number of patients with at least one event) and several adverse events were extracted. The following adverse events were considered: nausea, vomiting and diarrhoea. Furthermore, cases of pancreatitis, angioedema and cardiovascular events (defined as myocardial infarction, angina pectoris, coronary artery revascularization, chronic heart failure, stroke and arteriopathy of lower limbs) reported as serious or severe adverse events were considered, together with death for any cause.

Separate analyses were performed for trials with different GLP-1 receptor agonists, whenever possible.

Heterogeneity was calculated for placebo- and active comparator-controlled trials separately, using the I^2 statistics. Weighted mean differences were calculated for HbA1c and BMI and a random-effects model was used for the meta-analysis. Mantel–Haenszel odds ratio with 95% confidence interval (MH–OR) was calculated for hypoglycaemia, and the adverse events defined above, using a random-effects model. Publication/disclosure bias was estimated separately for placebo-controlled trials and studies versus active comparators, using the Begg and Mazumdar rank correlation test; Kendall's tau without continuity correction, and one-sided *P*, were calculated. Although the risk of bias due to defects of conduct of randomized trial has been reported to be low for studies investigating the effect of drugs on objective outcomes (12), separate analysis was performed on placebo-controlled trials in order to verify the possible bias associated with inadequate allocation concealment or randomization procedure. All those analyses were performed using comprehensive meta-analysis version 2, Biostat, (Englewood, NJ, USA) and SPSS 16.0. Interaction was assessed using the method described by Altman and Bland (13). The statistical power of the meta-analysis to detect a clinically relevant difference (at least 0.5%) in HbA1c for placebo-controlled and active-comparator trials was assessed, with the method described by Thorlund (14). The bias associated with accumulation of data was explored by calculating weighted mean reduction of HbA1c and *z* values separately for trials published before 2005, 2006, 2007, 2008 and 2009 (15).

Results

The Medline and EMBASE search provided 599 and 43 randomized clinical trials; all the articles retrieved on EMBASE had already been identified through Medline.

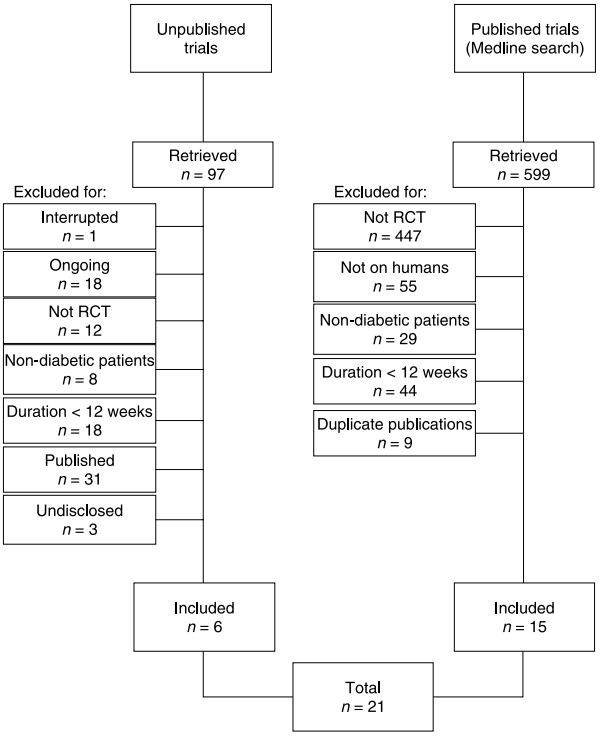

Figure 1 Trial flow diagram. RCT, randomized clinical trial.

A further Cochrane search yielded 44 hits, out of which four were not randomized clinical trials, seven were duplicate publications, one was a trial performed in non-diabetic subjects and 19 were short-term trials; the remaining 13 trials had already been identified through Medline. The trial flow is summarized in Fig. 1, and the characteristics of the trials included in the meta-analysis are summarized in Table 1. Among the trials included, 14 were described in publications on peer-reviewed journals; results of five unpublished trials were disclosed on different websites, or in abstracts from ADA and/or EASD 2008 congresses, while two trials, still unpublished at the time of trial selection, became available in peer-reviewed journals during the process of manuscript preparation. Furthermore, one unpublished trial (CT register 9697) was published during the process of preparation of the manuscript, and included in the meta-analysis (16). Among the 21 trials included in the analysis enrolling 8482 patients (5429 with GLP-1 receptor agonists and 3053 with active comparators or placebo), 12 were placebo-controlled and six were active comparator studies; the remaining three studies had two comparator arms, versus placebo and active drugs. Furthermore, three completed unpublished trials, the results of which were undisclosed, could be identified; for one of those (NCT00381342), results were published during the revision of the manuscript and could be included in the analysis, The remaining two trials (NCT00375492 and NCT00313001) explored the effect of exenatide bis in die (b.i.d.) for 24 weeks versus placebo (NCT00375492) or insulin (NCT00313001), in combination with sulphonylureas and/or metformin (NCT00375492 and NCT00313001). The number of patients planned was 190 and 540 for NCT00375492 and NCT00313001 respectively.

In order to retrieve undisclosed data, an attempt was made at reaching through email the principal investigators of 14 of the studies included in the analysis. Out of the 14 requests, eight remained unanswered, despite the correct delivery of the e-mail message (and the fact that the message had actually been read in most cases). Out of the remaining six investigators, four clarified that the request for the disclosure of data had to be addressed to the sponsor, while two declined the invitation for other reasons. The sponsors were addressed the same request, which remained unanswered. Therefore, this attempt did not allow the retrieval of any additional information.

Publication bias and heterogeneity

Considering HbA1c as the main outcome variable, Begg and Mazumdar rank correlation test was applied to verify publication/disclosure bias. Kendall's tau was

Table 1 Characteristics of the studies included in the meta-analysis.

Study (references)	Dose	Comparator	Add on to	Randomization	Blinding	Drop-out	Intention-to-treat
GLP-1 analogues							
Liraglutide	mg/die						
Madsbad (9)	0.045–0.75	Glimepiride	None	NA	OL	A	Yes
	0.045–0.75	Placebo	None	NA	OL	A	Yes
Vilsboll (3)	0.65–1.90	Placebo	None	NA	NA	A	Yes
Seino (10)	0.1–0.9	Placebo	None	A	A	A	Yes
Feinglos (8)	0.045–0.75	Metformin	None	NA	NA	A	No
Garber (22)	1.2–1.8	Glimepiride	None	A	A	A	Yes
Nauck (23)	1.2–1.8	Placebo	Metformin	A	A	A	Yes
		Glimepiride	Metformin	A	A	A	Yes
LEAD-1	1.2–1.8	Placebo	SU	–	–	–	Yes
LEAD-4	1.2–1.8	Placebo	TZD + Met	–	–	–	Yes
LEAD-5	1.8	Placebo	SU + Met	–	–	–	Yes
	1.8	Glargine	SU + Met	–	–	–	Yes
Exenatide	μg/die						
Davis (24)	20	Insulin	SU/Met	NA	OL	A	Yes
Barnett (25)	20	Insulin	SU/Met	A	OL	A	Yes
Nauck (26)	20	Insulin	SU + Met	A	OL	A	Yes
Heine (27)	20	Insulin	SU + Met	A	OL	A	Yes
DeFronzo (28)	10–20	Placebo	Metformin	NA	A	A	Yes
Zinman (29)	20	Placebo	TZD ± Met	A	A	A	Yes
Buse (30)	20	Placebo	SU	NA	NA	A	Yes
Kendall (31)	10–20	Placebo	SU + Met	NA	A	A	Yes
CT Register 8683	5–10–20	Placebo	SU ± Met/TZD	NR	NR	NR	Yes
Gao (16)	20	Placebo	SU ± Met	A	A	A	Yes
Kim (32)[a]	0.8–2[a]	Placebo	Met/None	A	A	A	Yes
Moretto (33)	10–20	Placebo	None	A	A	A	Yes

NA, not adequate; A, adequate; OL, open label; NR, not reported; SU, sulphonylureas; Met, metformin; TZD, thiazolidinediones; −, information not available; ±, and/or; /, or.
[a]Exenatide long-acting release (mg/wk).

−0.25 ($P=0.11$) and 0.14 ($P=0.36$) for placebo- and active comparator-controlled trials respectively; the corresponding figures for published trials only were −0.28 ($P=0.15$) and 0.07 ($P=0.43$) respectively.

I^2 for HbA1c was 83.6 and 83.2 for placebo- and active comparator-controlled trials respectively (both $P<0.001$).

Efficacy

The metabolic effects of GLP-1 receptor agonists observed in clinical trials included in the meta-analysis are summarized in Table 2. The reduction of HbA1c observed in placebo-controlled trials was significantly greater than that reported in active-comparator studies (test for interaction: $z=4.54$, $P<0.001$). The statistical power to detect a 0.5% difference in HbA1c at endpoint was >0.99 for placebo-controlled trials and for comparative studies versus sulphonylureas and insulin, whereas the corresponding figure for the only one available metformin-controlled trial was 0.65. In placebo-controlled trials, GLP-1 receptor agonists determined a significant reduction of HbA1c (Fig. 2); similar results were obtained when meta-analyzing separately trials with exenatide b.i.d. or liraglutide once a day (o.a.d., Fig. 3). After the exclusion of one trial (10) in which the drug was used at submaximal doses (<1 vs 1.2–1.8 mg/day of the other trials), liraglutide reduced HbA1c by −1.0 (−1.1, −0.8) ($P<0.001$) in comparison with placebo. Separate analyses were not performed for exenatide long-acting release formulation, due to the small number of available trials. The effects of GLP-1 receptor agonists on HbA1c were similar in shorter- and longer-term trials (Fig. 3). The reduction of HbA1c in unpublished trials (−1.0 (−1.1, −0.9); $P<0.001$) was similar to that obtained in published trials (−0.9 (−1.1, −0.7); $P<0.001$). Furthermore, the effect of GLP-1 receptor agonists on HbA1c in published placebo-controlled trials which did not report satisfactorily randomization procedures ($n=5$; −0.8 (−1.1, −0.5); $P<0.001$) was not superior (test for interaction: $z=1.07$, $P=0.14$) to those trials which adequately described this feature ($n=6$; −1.1 (−1.3, −0.8); $P<0.001$); similarly, HbA1c reduction in placebo-controlled trials with inadequate description of allocation concealment ($n=3$; −0.8 (−1.5, −0.1); $P<0.001$) was similar ($z=0.13$, $P=0.023$) to that of the other, more properly reported, trials ($n=8$; −1.0 (−1.2, −0.8); $P<0.001$). The reduction of HbA1c in placebo controlled trials published before 2005, 2006, 2007, 2008 and 2009 ($n=1$, 4, 4, 7, and 9 respectively) were −0.1(−0.5, 0.3), −0.7(−0.9, −0.4), −0.7(−0.9, −0.4),

Table 2 Moderators and outcome variables in individual studies included in the meta-analysis.

Study (references)	Number of patients (ID/C)	Comparator	Trial duration (wks)	Age[a] (ys)	Duration of DM[a] (ys)	HbA1c baseline[a] (%)	HbA1c endpoint (%, ID/C)	BMI baseline[a] (kg/m^2)	BMI endpoint (kg/m^2)
Liraglutide									
Madsbad (9)	135/26	Glimepiride	12	57	4.5	7.5	7.2/7.2	30.4	NR
	135/29	Placebo	12	57	4.5	7.5	7.2/7.3	30.4	NR
Vilsboll (3)	123/40	Placebo	14	55	5.0	8.3	7.0/8.5	30.0	NR
Seino (10)	180/46	Placebo	14	57	8.0	8.3	7.0/8.5	23.9	23.6/23.3
Feinglos (8)	176/34	Metformin	12	53	4.7	7.0	7.6/6.9	34.5	34.4/33.7
Garber (22)	498/248	Glimepiride	52	53	5.4	8.3	7.3/7.8	33.1	32.4/33.5
Nauck (23)	724/121	Placebo	26	57	7.9	8.4	7.6/8.6	31.0	30.2/31.1
	724/242	Glimepiride	26	57	7.4	8.4	7.6/7.5	31.0	30.2/31.3
LEAD-1	695/115	Placebo	26	56	7.9	8.4	7.7/8.7	30.0	30.1/30.0
LEAD-4	356/177	Placebo	26	55	9.2	8.5	7.0/7.9	33.5	33.0/33.7
LEAD-5	230/119	Placebo	26	57	9.4	8.2	7.0/8.1	30.5	29.9/30.4
	230/232	Glargine	26	57	9.4	8.2	7.0/7.2	30.5	29.9/31.1
Exenatide									
Davis (24)	33/16	Insulin	16	53	11.0	8.1	8.4/8.2	34.0	31.5/35.1
Barnett (25)	136/127	Insulin	16	55	7.4	8.9	7.5/7.5	31.1	30.2/32.1
Nauck (34)	253/248	Insulin	52	59	9.9	8.6	7.7/7.6	30.4	29.7/31.3
Heine (27)	282/267	Insulin	26	59	9.5	8.2	7.2/7.1	31.3	30.6/32.0
DeFronzo (28)	223/113	Placebo	30	53	5.8	8.2	7.6/8.3	34.0	33.2/33.9
Zinman (29)	121/112	Placebo	16	56	7.7	7.9	7.0/8.0	34.0	33.4/33.9
Buse (30)	248/129	Placebo	30	55	6.3	8.6	7.9/8.7	33.3	33.1/33.2
Kendall (31)	486/247	Placebo	30	55	9.0	8.5	7.8/8.6	34.0	32.9/33.7
CT Register 8683	111/40	Placebo	12	61	11.8	NR	NR	25.1	NR
Gao (16)	234/232	Placebo	16	NR	NR	8.3	7.3/8.1	NR	NR
Kim (32)[b]	30/15	Placebo	15	54	5.0	8.5	6.9/9.0	36.0	34.9/36.0
Moretto (33)	155/78	Placebo	24	54	2.0	7.8	7.0/7.6	32.0	30.4/31.4

ID/C, investigational drug/comparator; DM, diabetes mellitus; wks, weeks; ys, years; BMI, body mass Index; NR, not reported.
[a]Mean values between ID and C groups.
[b]Exenatide long-acting release.

Study	Difference in means	Standard error	Variance	Lower limit	Upper limit	*z* value	*P* value
Buse (30)	−0.800	0.123	0.015	−1.042	−0.558	−6.492	0.000
Gao (16)	−0.800	0.107	0.011	−1.009	−0.591	−7.503	0.000
DeFronzo (28)	−0.700	0.115	0.013	−0.926	−0.474	−6.062	0.000
Kendall (31)	−0.800	0.078	0.006	−0.953	−0.647	−10.238	0.000
Zinman (29)	−1.000	0.112	0.013	−1.219	−0.781	−8.936	0.000
Kim (32)	−2.100	0.381	0.145	−2.847	−1.353	−5.507	0.000
Madsbad (9)	−0.100	0.212	0.045	−0.516	−0.316	−0.471	0.638
Vilsboll (3)	−1.500	0.141	0.020	−1.777	−1.223	−10.607	0.000
Seino (10)	−1.500	0.160	0.026	−1.813	−1.187	−9.382	0.000
Moretto (33)	−0.600	0.154	0.024	−0.902	−0.298	−3.897	0.000
LEAD-1	−1.000	0.131	0.017	−1.257	−0.743	−7.641	0.000
Nauck(LEAD-2) (23)	−1.000	0.112	0.012	−1.219	−0.781	−8.959	0.000
LEAD-4	−0.900	0.108	0.012	−1.111	−0.689	−8.363	0.000
LEAD-5	−1.100	0.125	0.016	−1.346	−0.854	−8.767	0.000
Overall	−0.953	0.080	0.006	−1.109	−0.796	−11.921	0.000

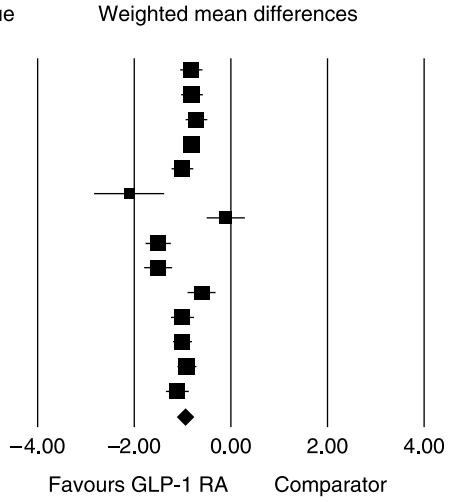

Figure 2 Weighted differences (with 95% CI) of mean HbA1c at endpoint across placebo-controlled trials.

−0.9(−1.2, −0.7), −0.6(−0.9, −0.3)%, with *z* values of −0.47, −5.97, −5.97, −6.54, and −3.90 respectively. When the two trials published in 2009 were added, HbA1c reduction was −1.0(−1.1, −0.8)%, with a *z* value of −9.00, while the corresponding figure for all trials (including those still unpublished) were −1.0(−1.1, −0.8)% and −11.92.

Trials comparing GLP-1 receptor agonists with other active drugs are summarized in (Fig. 4). GLP-1 receptor agonists were compared with insulin in five trials, showing no significant difference in efficacy on HbA1c (Fig. 3). In comparison with insulin, GLP-1 receptor agonists, which were available only in four exenatide trials, significantly reduced self-monitored 2 h post-prandial glucose after breakfast (−0.67 (−0.56, −0.78) mmol/l; $P<0.001$) and dinner (−0.66 (−1.14, −2.73) mmol/l; $P<0.001$), but not lunch (0.19 (−0.03, 0.42); $P=0.092$).

In three trials, a GLP-1 receptor agonist (liraglutide) was compared with sulphonylureas (glimepiride), with no significant difference in HbA1c at endpoint (Fig. 3). Only one trial compared liraglutide with metformin, not allowing any meta-analysis.

Body weight

GLP-1 receptor agonists led to a significant reduction of BMI, in comparison with placebo (−0.44 (−0.78, −0.10) kg/m^2; $P=0.012$; 11 trials). With respect to placebo, difference in endpoint BMI was −0.62 (−1.14, −0.10) kg/m^2 ($P=0.021$) and −0.30 (−0.75, 0.16) kg/m^2 ($P=0.24$) for exenatide b.i.d. and liraglutide o.a.d. respectively. After the exclusion of one trial (10) in which the drug was used at submaximal doses, the difference in endpoint BMI between liraglutide and placebo was −0.47 (−1.00, 0.05) kg/m^2 ($P=0.077$).

In comparison with insulin, GLP-1 receptor agonists were associated with a significantly lower endpoint BMI (−1.57 (−1.98, −1.15) kg/m^2; $P<0.001$; 5 trials).

Safety: hypoglycaemia

Data on hypoglycaemic episodes were retrieved in 15 out of 21 trials. Hypoglycaemic episodes were reported by 434 patients (325 with investigational drug and 109 with comparator) enrolled in trials with exenatide b.i.d; the corresponding figures for liraglutide ($n=5$ trials) were 78 and 109 patients with investigational drug,

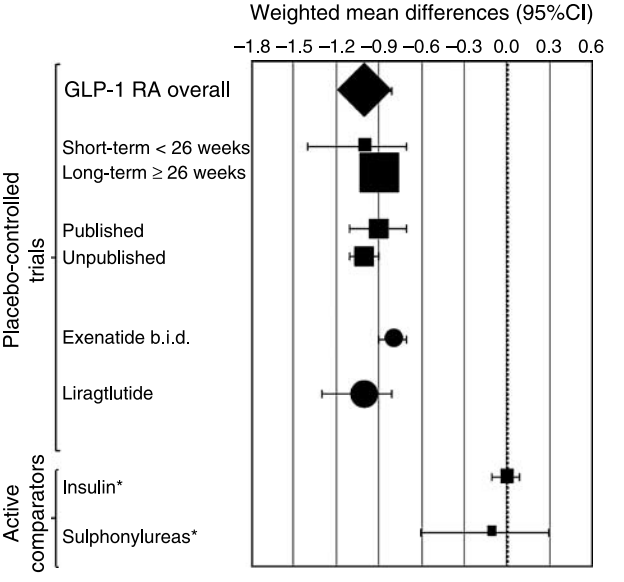

Figure 3 Weighted differences (with 95% CI) of mean HbA1c at endpoint. *GLP-1 receptor agonists versus insulin or sulphonylureas.

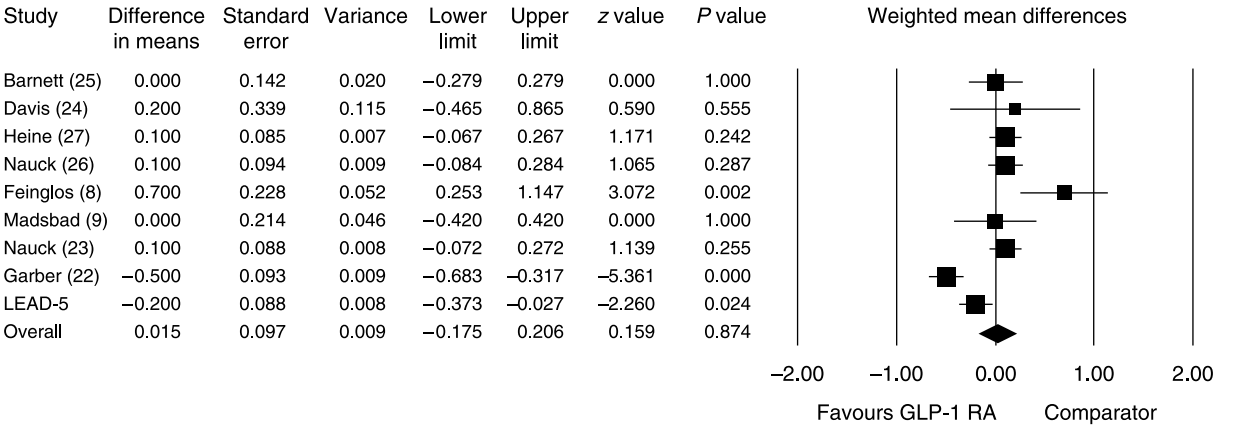

Figure 4 Weighted differences (with 95% CI) of mean HbA1c at endpoint across active comparator-controlled trials.

and with comparator respectively. In placebo-controlled trials, exenatide b.i.d. was associated with a significant increase in the proportion of patients experiencing hypoglycaemia (MH–OR 2.92 (1.49, 5.75); $P=0.002$); however, the excess hypoglycaemic risk associated with exenatide was observed only in trials in which the drug was combined with sulfonylureas (MH–OR 4.62 (1.89, 11.21), $P=0.001$ and 1.37 (0.72, 2.63), $P=0.34$, in trials with or without sulphonylureas respectively). When compared with insulin, exenatide b.i.d. was not associated with increased risk for hypoglycaemia (MH–OR 0.61 (0.33, 1.14), $P=0.125$).

Data on severe hypoglycaemic episodes were retrieved in all trials with exenatide b.i.d., and in eight out of nine trials with liraglutide. In trials with exenatide, severe hypoglycaemic episodes were reported by seven patients enrolled in placebo-controlled trials (five with active drug, two with placebo); in all those trials, exenatide was combined with sulphonylureas. In trials comparing exenatide with insulin, 12 patients experienced severe hypoglycaemia (five with exenatide, seven with insulin); the difference between the groups was not statistically significant (MH–OR 0.74 (0.23, 2.39); $P=0.61$). In the eight trials with liraglutide reporting data on severe hypoglycaemia, only one event was recorded (with liraglutide, in a trial comparing liraglutide with placebo, in combination with sulphonylureas).

Safety: other adverse events

Information on mortality was available for all trials, except for the unpublished trials with liraglutide ($n=3$). In trials with GLP-1 receptor agonists only five deaths (two with investigational drugs and three in comparator groups) were observed during the trials included in the meta-analysis.

The incidence of major cardiovascular events was described in 14 out of 21 trials. Twenty-four patients experienced a major cardiovascular event during trials with GLP-1 receptor agonists (Table 3); the MH–OR for cardiovascular events, in comparison with control groups, was 0.99 (0.52, 1.91) ($P=0.98$). The corresponding figure for placebo-controlled trials ($n=3$) was 0.46 (0.18–1.20), $P=0.11$.

Cases of pancreatitis were reported in three and one patients treated with liraglutide and glimepiride respectively. No cases of angioedema were reported. Information on pancreatitis and angioedema was available only for 12 trials. GLP-1 receptor agonists were associated with increased incidence of nausea, vomiting and diarrhoea (Table 4), both in comparison with placebo or insulin (data not shown).

Discussion

Physicians' knowledge of novel drugs is largely derived from the results of published clinical trials. Conversely, the registration of new compounds is based on the results of trials which may well remain unpublished. The decision to publish a trial is, in most instances, performed by the sponsor, who have a specific interest in pursuing the greater safety and tolerability of the new drug. The reluctance of most investigators to provide undisclosed data, despite a formal request from the authors of this meta-analysis, confirms that concealment of some results is difficult to overcome; however, the retrieval of all available information should always be attempted, although the possibility of including some information of poorer methodological quality should be taken into account.

A major strength of the present study is the inclusion of a substantially greater number of trials in comparison with previous similar meta-analyses (7), thanks to the availability of some recently published or still unpublished, but publicly disclosed (on different websites) studies. The availability of a larger number of studies reduces the impact of the reported heterogeneity of results across trials. The overall efficacy on HbA1c of GLP-1 agonists in placebo-controlled trials is similar to

Table 3 Adverse events in individual studies included in the meta-analysis.

Study (references)	Any hypos (n, ID/C)	Severe hypos (n, ID/C)	Nausea (n, ID/C)	Vomiting (n, ID/C)	Diarrhoea (n, ID/C)	CVD (n, ID/C)	Death (n, ID/C)
Liraglutide							
Madsbad (9)	1/4	0/0	NR	3/1	5/0	0/0	0/0
	1/0	0/0	NR	3/0	5/0	0/0	0/0
Vilsboll (3)	0/0	0/0	9/1	4/0	26/5	0/0	0/0
Seino (10)	0/0	0/0	NR	NR	NR	0/0	0/0
Feinglos (8)	5/2	0/0	7/2	4/1	NR	NR	0/0
Garber (22)	50/58	0/0	139/21	57/9	85/22	NR	0/1
Nauck (23)	22/4	0/0	290/21	44/1	88/4	NR	0/0
	22/41	0/0	290/42	44/2	88/8	NR	0/0
LEAD-1	NR	1/0	52/2	NR	NR	NR	NR
LEAD-4	NR	0/0	NR	NR	NR	NR	NR
LEAD-5	NR	NR	32/4	NR	NR	NR	NR
LEAD-5	NR	NR	32/3	NR	NR	NR	NR
Exenatide							
Davis (24)	13/6	1/0	16/2	8/1	8/0	1/0	0/0
Barnett (25)	20/32	0/3	58/4	13/4	4/3	0/0	0/0
Nauck (34)	NR	0/0	84/1	38/8	24/5	10/5	2/1
Heine (27)	NR	4/4	161/23	49/10	24/8	5/3	0/0
DeFronzo (28)	11/6	0/0	91/26	25/4	31/9	NR	0/0
Zinman (29)	13/8	NR	48/17	16/1	7/3	0/0	0/0
Buse (30)	54/4	0/0	115/9	29/3	25/5	1/2	0/0
Kendall (31)	114/31	1/0	213/51	69/11	67/16	7/6	0/1
CT Register 8683	NR	0/0	20/0	NR	NR	0/0	0/0
Gao (16)	83/21	2/1	NR	NR	NR	0/2	0/0
Kim (32)[a]	4/0	0/0	7/1	0/0	NR	0/0	0/0
Moretto (33)	7/1	0/0	12/0	6/0	2/0	0/0	0/0

Hypos, hypoglycaemia; ID/C, investigational drug/comparator; CVD, cardiovascular disease; NR, not reported.
[a]Exenatide long acting release.

that reported in a previous meta-analysis (7). However, the greater number of available studies allowed separate analyses of trials using different GLP-1 agonists.

Liraglutide is a novel compound, with similar effects as exenatide, but with more favourable kinetics, allowing a once-daily administration. Despite the fact that several trials with liraglutide have been completed, and included in files for registration submitted to the European authorities, few of these studies have been published so far (3, 8, 9). Furthermore, some of the published studies (8, 9) were performed with submaximal doses of the drug (less than 1 mg/day), while the optimal dose range is 1.2–1.8 mg/day. Therefore, if only published studies were considered, the efficacy of liraglutide could be underestimated (and its tolerability overestimated). The inclusion in the present meta-analysis of several large trials which have already been completed, and disclosed, although still unpublished, allows a more comprehensive assessment of the clinical profile of liraglutide.

Placebo-controlled trials with either exenatide or liraglutide in patient samples of similar characteristics suggest that the efficacy and tolerability of liraglutide should not be inferior to those of exenatide, with the

Table 4 Risk of adverse events with GLP-1 receptor agonists in comparison with control groups.

Adverse event	Number of cases		Number of trials[a]	MH–OR (95%, CI)	*P*
	ID	C			
Nausea					
GLP-1 receptor agonists	1354	230	17	3.88 (2.79, 5.42)	<0.001
Exenatide b.i.d	818	133	10	8.38 (4.27, 16.48)	<0.001
Liraglutide	522	69	6	3.48 (2.29, 5.28)	<0.001
Vomiting					
GLP-1 receptor agonists	365	56	14	4.23 (2.67, 6.13)	<0.001
Exenatide b.i.d	253	42	9	4.54 (3.24, 6.38)	<0.001
Liraglutide	108	11	5	4.26 (1.01, 18.07)	0.049
Diarrhea					
GLP-1 receptor agonists	396	88	14	2.36 (1.67, 3.33)	<0.001
Exenatide b.i.d	192	49	9	2.56 (1.85, 3.54)	<0.001
Liraglutide	204	35	5	2.36 (1.67, 3.33)	<0.001

ID, interventional drug; C, comparator.
[a]Trials with 0 events or without any information are not included.

advantage of a once-a-day administration. The only available head-to-head comparison between the two drugs (still unpublished, but disclosed at a congress) showed a small, but significant advantage on HbA1c for liraglutide over exenatide (17).

Exenatide has a relatively short duration of action; in fact, when administered at breakfast and dinner, it does not seem to reduce satisfactorily the glycaemic peak after lunch. It can be speculated that the longer duration of action of liraglutide, with respect to exenatide, could allow a more accurate control of post-prandial hyperglycaemia throughout the day; however, little data is available on the effects of liraglutide on glycaemic profile to draw any conclusion on this point. It has been reported that liraglutide has a lower immunogenicity than exenatide, with a reduced incidence of antibody formation (18); it is possible that high titres of specific antibodies could interfere with the efficacy of GLP-1 receptor agonists (19).

GLP-1 stimulates insulin secretion and inhibits glucagon production in a glucose-dependent manner, i.e. its effects are blunted when blood glucose reaches the lower limits of the normal range (20). Therefore, GLP-1 receptor agonists are expected to reduce glycaemia with a low hypoglycaemic risk. In fact, monotherapy does not increase the risk of hypoglycaemia in comparison with placebo. Not surprisingly, GLP-1 receptor agonists are associated with a higher incidence of hypoglycaemic episodes when administered in combination with sulphonylureas. However, the hypoglycaemic risk with GLP-1 receptor agonists could be lower than that observed with insulin, although the difference does not reach statistical significance.

The number of cases of severe hypoglycaemia reported in GLP-1 receptor agonist trials is negligible; all cases occurred in patients receiving combined treatment with sulphonylureas.

Among other expected adverse events, nausea, vomiting and diarrhoea are associated with GLP-1 receptor agonists. In this respect, the results of the meta-analysis do not add further information to that reported in individual trials. Interestingly, no case of acute pancreatitis has ever been reported in trials with those drugs.

The introduction of a new class of drugs that are designed for long-term use always raises some concerns about safety during prolonged treatment. The possibility of rare, unexpected serious adverse events, which could not be detected in registration trials, should be considered. Meta-analyses of all available studies, including post-registrative trials, can add some relevant information in this respect. The number of reported deaths in available trials is still very small; however, there is no evidence suggesting an increase in mortality during treatment with GLP-1 receptor agonists. The number of cardiovascular events registered in clinical trials is remarkably greater, although still inadequate to detect minor differences between groups. It should be considered that the duration of the available trials (up to 1 year) is insufficient to detect any effect of treatment (either detrimental or beneficial) on atherogenesis.

The new Consensus algorithm recently issued by ADA/EASD suggests that GLP-1 receptor agonists can be used, in selected cases, as an add-on treatment to metformin (21). Available data summarized in the present meta-analysis suggest that liraglutide could be a valid alternative to exenatide in these same patients.

In conclusion, GLP-1 receptor agonists are effective in reducing HbA1c and post-prandial glucose. In patients failing to sulphonylureas and/or metformin, GLP-1 receptor agonists are similarly effective as insulin. The safety profile is reassuring, with low hypoglycaemic risk, and no evidence of detrimental effects on cardiovascular disease. GLP-1 receptor agonists, which induce weight loss, produce some gastrointestinal side effects. Available data suggest that the efficacy and tolerability of the novel agent, liraglutide, which is adequate for once-a-day administration, are comparable with those of exenatide b.i.d.

Declaration of interest

Dr Matteo Monami (MD, PhD) has the following conflicts of interest:

1) speaking fees from Guidotti, Eli Lilly, Merck Sharpe & Dome, Menarini and Takeda.

2) consultancy fees from Sanofi Aventis and Menarini.

Dr Edoardo Mannucci (MD) has the following conflicts of interest:

1) speaking fees from Abiogen Pharma, Glaxo-Smith-Kline, Guidotti, Eli Lilly, Menarini, Merck Sharp & Dome, Merck KgA, Novo Nordisk, Novartis, Sanofi Aventis and Takeda.

2) consultancy fees from Novartis, Novo Nordisk and Sanofi Aventis.

3) research grants from Novartis, Novo Nordisk, Sanofi Aventis and Takeda.

Dr Mannucci had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prof. Niccolò Marchionni (MD) has the following conflicts of interest:

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