Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial

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Summary

Background New treatments for type 2 diabetes mellitus are needed to retain insulin–glucose coupling and lower the risk of weight gain and hypoglycaemia. We aimed to investigate the safety and efficacy of liraglutide as monotherapy for this disorder.

Methods In a double-blind, double-dummy, active-control, parallel-group study, 746 patients with early type 2 diabetes were randomly assigned to once daily liraglutide (1·2 mg [n=251] or 1·8 mg [n=247]) or glimepiride 8 mg (n=248) for 52 weeks. The primary outcome was change in proportion of glycosylated haemoglobin (HbA_{1c}). Analysis was done by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NTC00294723.

Findings At 52 weeks, HbA_{1c} decreased by 0·51% (SD 1·20%) with glimepiride, compared with 0·84% (1·23%) with liraglutide 1·2 mg (difference –0·33%; 95% CI –0·53 to –0·13, p=0·0014) and 1·14% (1·24%) with liraglutide 1·8 mg (–0·62; –0·83 to –0·42, p<0·0001). Five patients in the liraglutide 1·2 mg, and one in 1·8 mg groups discontinued treatment because of vomiting, whereas none in the glimepiride group did so.

Interpretation Liraglutide is safe and effective as initial pharmacological therapy for type 2 diabetes mellitus and leads to greater reductions in HbA_{1c}, weight, hypoglycaemia, and blood pressure than does glimepiride.

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Introduction

Type 2 diabetes mellitus is a progressive disease; many treatments work early in the course of disease but do not remain effective.[1,2] Glucagon-like peptide 1 (GLP-1) stimulates glucose-dependent insulin secretion, suppresses glucagon secretion, and moderates appetite by delaying gastric emptying and reducing hunger.[3] Endogenous GLP-1 has a very short half-life (1·5 min) because of rapid degradation by dipeptidyl peptidase 4,[3] which restricts its therapeutic usefulness. Liraglutide is an analogue of human GLP-1 with 97% homology to the endogenous protein[4] and a half life of 13 h, which gives it a pharmacokinetic profile suitable for once daily treatment.[5]

Liraglutide restores glucose-dependent insulin secretion after one injection in patients with type 2 diabetes mellitus.[6] In a 14 week monotherapy trial,[7] treatment with liraglutide produced substantial and clinically significant reductions in fasting and postprandial glucose concentrations and glycosylated haemoglobin (HbA_{1c}), resulted in moderate weight loss, and had a very low risk of hypoglycaemia. Common side-effects of liraglutide treatment include gastrointestinal side-effects, such as nausea, diarrhoea, and vomiting.

We investigated the safety and efficacy of two doses of liraglutide versus glimepiride over 52 weeks for treatment of type 2 diabetes mellitus. We studied patients thought to be in the early stages of disease because they were either drug-naive, treated with lifestyle modifications, or had failed to achieve control with a single oral drug at less than 50% of maximum approved dose.

Methods

Participants and study design

Participants were aged 18–80 years, had body-mass index of 45 kg/m² or less, and were diagnosed with type 2 diabetes mellitus. Eligible patients had been treated with diet and exercise (36·5% of patients randomised) or up to half the highest dose of oral antidiabetic drug monotherapy (63·5%) including sulphonylureas, meglitinides, aminoacid derivatives, biguanides, α-glucosidase inhibitors, and thiazolidinediones (1500 mg metformin or 30 mg pioglitazone were allowed) for at least 2 months. Patients had a screening HbA_{1c} value of 7–11% if treated with diet and exercise or 7–10% with oral antidiabetic monotherapy.

Exclusion criteria were insulin treatment during the previous 3 months (except short-term treatment for intercurrent illness), treatment with systemic corticosteriods, hypoglycaemia unawareness or recurrent severe hypoglycaemia, and impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations ≥2·5 times upper normal range). Local institutional review boards approved the protocol, and all patients provided written informed consent before initiation of any trial-related activities. The study was done in accordance with the Declaration of Helsinki[8] and

Good Clinical Practice guidelines.[9] This trial is registered with ClinicalTrials.gov, number NTC00294723.

This trial was a 52-week, phase III, multicentre (126 sites in the USA and 12 sites in Mexico), double-blind, double-dummy, active-control, parallel-group study. Patients were randomly assigned (1:1:1) to receive once daily subcutaneous liraglutide 1·2 mg or 1·8 mg or once daily oral glimepiride 8 mg, and stratified by baseline diabetes treatment (diet and exercise *vs* oral antidiabetic monotherapy). Previous treatment with oral antidiabetic drugs was discontinued at randomisation. After randomisation, patients underwent forced titration: doses of liraglutide were increased every week from 0·6 mg to 1·2 mg to 1·8 mg and glimepiride (or placebo) was increased over 2 weeks (2 mg to 4 mg to 8 mg). Glimepiride (active and placebo) was to be taken orally once daily in the morning before or with the first meal of the day. Liraglutide (active or placebo) was injected once daily at any time of day in the upper arm, abdomen, or thigh with a prefilled pen injection device with 30 gauge or 31 gauge needle. Participants were encouraged to inject liraglutide at the same time each day. Doses of study drugs were maintained for 52 weeks, including the titration period.

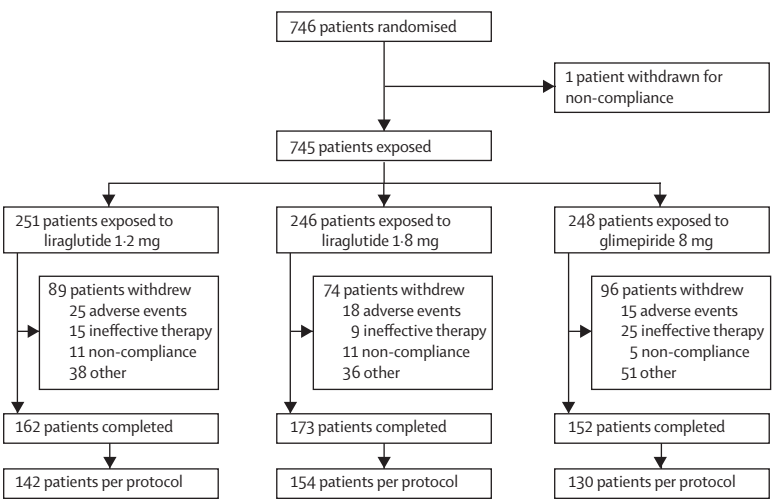

Figure 1: **Trial profile**
Analyses were done on the intention-to-treat population exposed to at least one dose of treatment. *Patient withdrawn from liraglutide 1·8 mg group before exposure.

	Liraglutide 1·2 mg	Liraglutide 1·8 mg	Glimepiride 8 mg
Randomised (ITT population)	251	247	248
Men	117 (47%)	121 (49%)	133 (54%)
Age (years)	53·7 (11·0)	52·0 (10·8)	53·4 (10·9)
Race			
White	200 (80%)	186 (75%)	197 (77%)
Black	34 (14%)	30 (12%)	30 (12%)
Asian	5 (2%)	12 (6%)	9 (4%)
Other	12 (5%)	19 (7%)	7 (7%)
Hispanic or Latin American ethnicity	81 (32%)	87 (35%)	93 (38%)
Body mass index (kg/m²)	33·2 (5·6)	32·8 (6·3)	33·2 (5·6)
Weight (kg)	92·5 (19·2)	92·8 (20·7)	93·4 (19·2)
Duration of diabetes (years)	5·2 (5·5)	5·3 (5·1)	5·6 (5·1)
Prestudy treatment			
Diet and exercise	91 (36%)	87 (35%)	94 (38%)
Oral antidiabetic monotherapy	160 (64%)	160 (65%)	154 (62%)
HbA_{1c} (%)	8·3% (1·0%)	8·3% (1·1%)	8·4% (1·2%)
Fasting plasma glucose (mmol/L)	9·3 (2·6)	9·5 (2·6)	9·5 (2·6)
Postprandial plasma glucose (mmol/L)	11·3 (2·4)	11·4 (2·5)	11·4 (2·7)
Systolic blood pressure (mm Hg)	127·6 (14·3)	128·1 (13·9)	130·0 (16·1)
Diastolic blood pressure (mm Hg)	78·5 (8·3)	78·8 (8·4)	79·5 (8·6)

Data are mean (SD) or n (%) unless otherwise noted. ITT=intention to treat.

Table 1: **Demographic and baseline characteristics**

Randomisation was done with telephone-based or web-based systems. Participants were randomly assigned to the lowest available number. Recruitment began on Feb 7, 2006, with the last patient visit for this portion of the study on Nov 7, 2007. Participants completing the study could enrol, subject to eligibility, into a continuing, open-label extension period.

The primary outcome was change in value of HbA_{1c} from baseline to 52 weeks. Secondary outcomes included changes in body weight, fasting plasma glucose, self-measured eight-point plasma-glucose profiles (measured before each meal, 90 min after the start of each meal, at bedtime, and at 0300 h), blood pressure, B-cell function (proinsulin to insulin ratio and two models of B-cell function: homoeostasis model assessment [HOMA]-B and HOMA-IR [insulin resistance]), fasting glucagon, and patients' reported assessment of quality-of-life. Laboratory analyses were done by central laboratories (MDS Pharma Services in Canada, Germany, and Switzerland). Participants used MediSense Precision Xtra/MediSense Optium (Abbott Diagnostics Inc, Abbott Park, IL, USA) glucose metres calibrated to plasma glucose to determine self-measured plasma glucose and recorded these values in diaries. Patients' reported outcome measures were developed by the validated Phase V Health Outcomes Information System (Phase V Technologies Inc, Wellesley Hills, MA, USA). A self-administered questionnaire was completed at randomisation and at weeks 28 and 52.

Key safety assessments were tolerability (including nausea and other gastrointestinal adverse events), serum calcitonin, and hypoglycaemic episodes (defined as measured plasma glucose <3·1 mmol/L). We defined self-treated episodes of hypoglycaemia as minor and those that needed third-party assistance as major. Calcitonin concentrations were measured on the basis of C-cell tumour findings in the rodent carcinogenicity studies (Novo Nordisk, unpublished) with liraglutide.

Statistical analysis

163 participants were needed in each group to achieve 85% of power to detect a difference of 0·4% in HbA_{1c}, (SD of 1·2% and a two-sample one-sided α of 0·025). With the assumption of a 30% drop-out rate, we enrolled

702 subjects (234 per arm). Furthermore, this sample size would be large enough to detect differences in bodyweight between treatment groups (3% of difference in percent change from baseline).

Analysis of efficacy outcomes was based on the intention-to-treat population, defined as participants exposed to at least one dose. Each endpoint was analysed with an ANCOVA model with treatment, country, and previous antidiabetic treatment as fixed effects, and baseline as the covariate. Missing data were imputed with last observation carried forward.

To reduce type 1 error, we did hierarchical tests for non-inferiority and superiority of liraglutide. We also compared the two dose groups of liraglutide, although this analysis was in addition to the primary analysis of comparison to glimepiride. Other efficacy endpoints were analysed with the ANCOVA model described above. The proportions of patients achieving HbA_{1c} targets (American Diabetes Association: <7%; International Diabetes Federation/American Association of Clinical Endocrinologists: ≤6·5%) were compared between treatments with a logistic regression model with treatment and baseline HbA_{1c} as covariates. Hypoglycaemic episodes were analysed with a generalised linear model that included treatment and country as fixed effects. Other safety data were compared with descriptive statistics. Results are means (SD) unless otherwise noted.

Role of funding source

The study was funded by Novo Nordisk, the manufacturer of liraglutide. In collaboration with the investigators, Novo Nordisk was responsible for the study design, protocol, statistical analysis plans and analysis, oversight, and reporting of results. Data were recorded at participating clinical centres and maintained by the sponsor. The LEAD-3 monotherapy study group had full access to the data. The authors had final responsibility for the decision to submit for publication.

Results

The three treatment groups were well balanced at baseline (figure 1, table 1). In the liraglutide treatment groups, most participants who withdrew did so because of other reasons or adverse events, whereas in the glimepiride group, other or ineffective therapy were the most common reasons for withdrawal. Mean baseline HbA_{1c} and fasting plasma glucose values were 8·2% and 9·5 mmol/L, respectively. Mean baseline weight was 92·6 kg and mean blood pressure was 129/79 mm Hg.

HbA_{1c} values decreased from baseline by 0·84% (SD 1·23) with liraglutide 1·2 mg, 1·14% (1·24) with liraglutide 1·8 mg, and 0·51% (1·20) with glimepiride. Decreases in proportion of HbA_{1c} in the liraglutide treatment groups were significantly greater than those in the glimepiride group, as shown by the differences between glimepiride and liraglutide 1·8 mg of –0·62% (95% CI –0·83 to –0·42, p<0·0001) and liraglutide 1·2 mg of –0·33% (–0·53 to –0·13, p=0·0014). Additionally, the reduction with liraglutide 1·8 mg was significantly

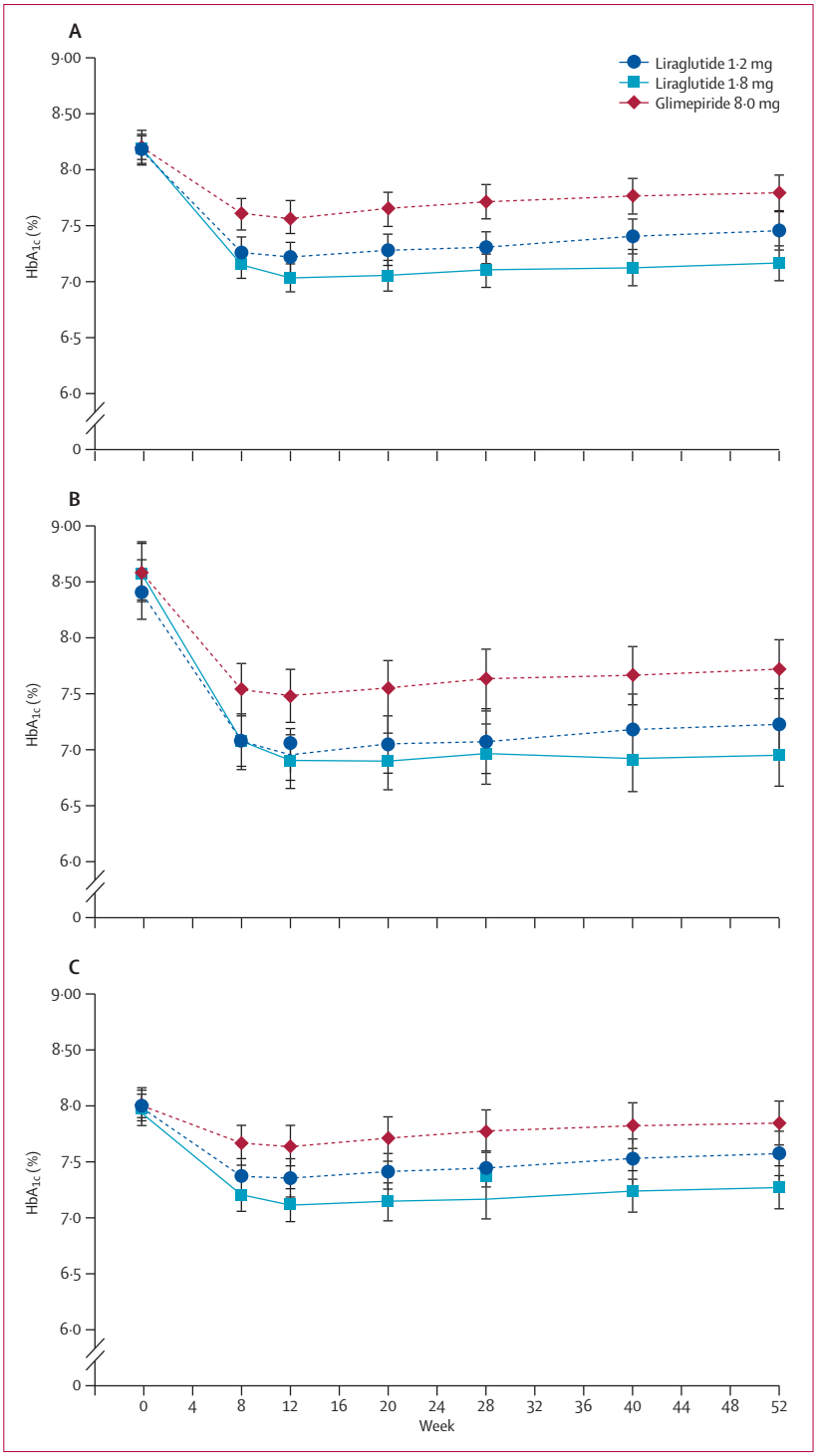

Figure 2: **Efficacy of glycaemic control shown by HbA_{1c} profiles**
(A) all particpants. (B) drug-naive participants. (C) participants previously treated with one oral antidiabetic drug. Data are mean (SE).

greater than that with liraglutide 1·2 mg (–0·29%; –0·50 to –0·09, p=0·0046).

Figure 2 shows mean HbA_{1c} values over time for all participants (all points after baseline with last observation carried forward) and for those previously treated with diet and exercise or monotherapy. HbA_{1c} values generally decline over the first 8–12 weeks of treatment. From week 12 to week 52, HbA_{1c} values increased slightly but significantly for participants treated with liraglutide 1·2 mg (p=0·0071) and glimepiride (p=0·0006); however, HbA_{1c} values had not changed significantly at week 52 with liraglutide 1·8 mg (p=0·33). Participants previously treated with diet and exercise had greater decreases in HbA_{1c} than did those switched from an oral antidiabetic drug to liraglutide (table 2). Participants who had never had any antidiabetic drugs and those previously treated showed significant decreases in HbA_{1c} after starting liraglutide.

At the end of the study, 28% of participants treated with liraglutide 1·2 mg and 38% treated with liraglutide 1·8 mg reached the International Diabetes Federation/

	Diet and exercise	Oral antidiabetic monotherapy
Liraglutide 1·2 mg	–1·19% (0·15)*	–0·47% (0·10)†
Liraglutide 1·8 mg	–1·60% (0·15)‡	–0·71% (0·09)‡
Glimepiride	–0·88% (0·13)	–0·17% (0·08)

Data are mean (SE). Compared with change with glimepiride *p=0·0234, †p=0·0215, and ‡p<0·0001.

Table 2: **Decreases in HbA_{1c} at 52 weeks for each trial intervention by previous treatment**

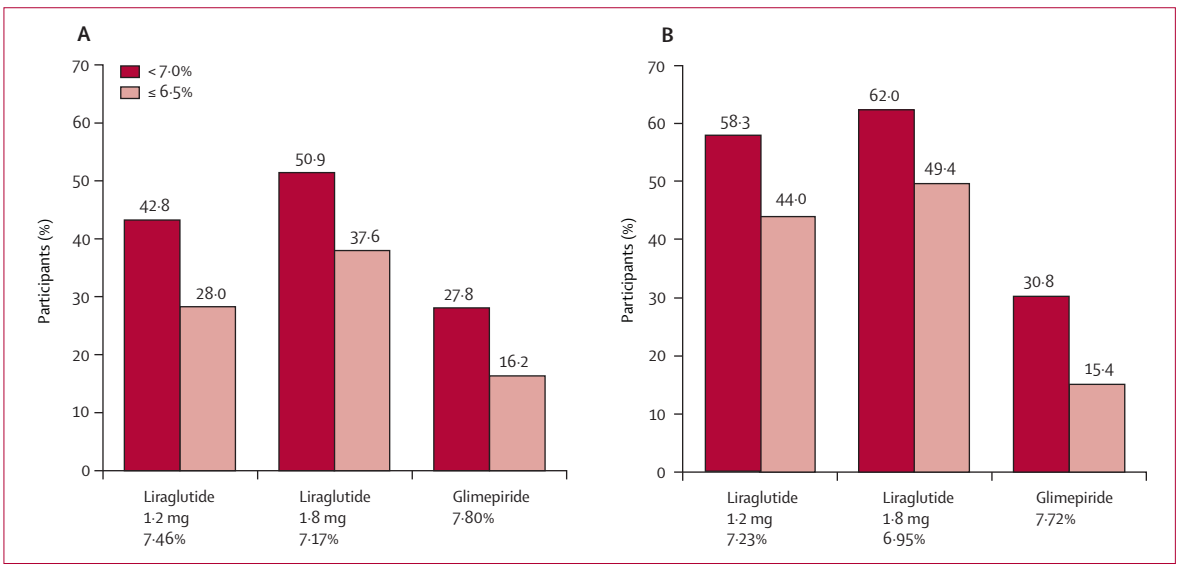

Figure 3: **Participants achieving HbA_{1c} targets of less than 7·0% (ADA) and less than or equal to 6·5% (IDF/AACE)**
(A) all participants. (B) drug-naive participants. Percentages under each treatment group are mean final HbA_{1c} values.

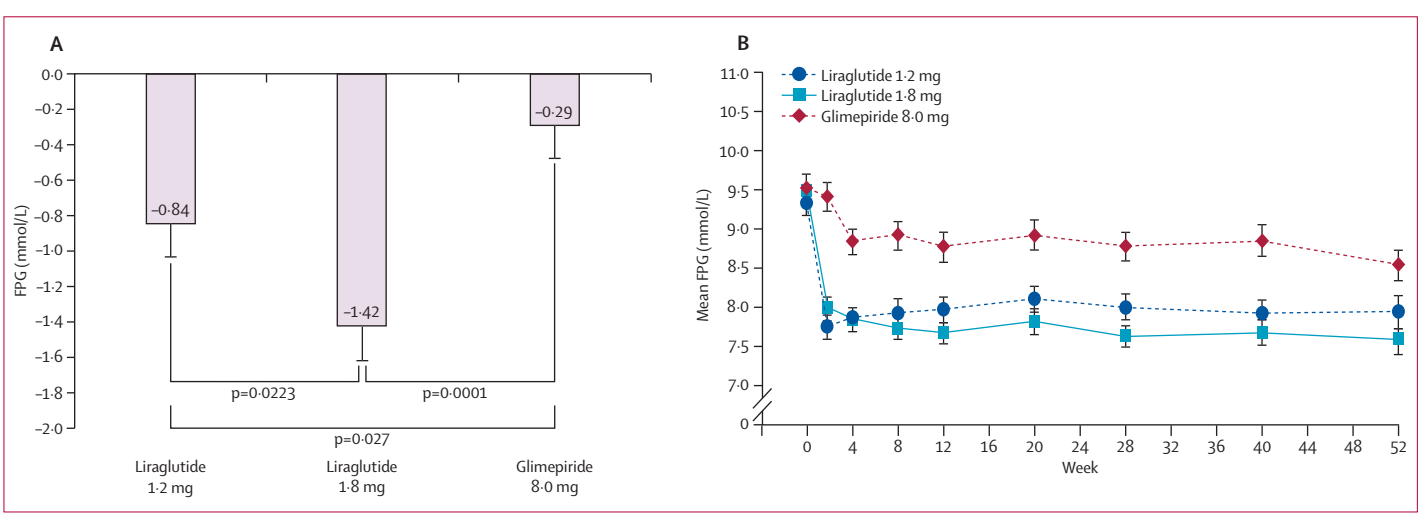

Figure 4: **Change in fasting plasma glucose (FPG)**
Data from laboratory values: difference from baseline to end-of-study with last observation carried forward (A) and change over time (B). Data are mean (SE).

American Association of Clinical Endocrinologists target HbA_{1c} of 6·5% or less, compared with 16% in those on glimepiride (p=0·0025 and p<0·0001 for liraglutide 1·2 mg and 1·8 mg, respectively; figure 3). Although participants previously treated with diet and exercise had higher baseline HbA_{1c} values, a greater proportion achieved the HbA_{1c} target (figure 3) than did those previously treated with oral antidiabetic monotherapy. Overall, compared with 28% in the glimepiride group, 43% of participants treated with liraglutide 1·2 mg (p=0·0007) and 51% on liraglutide 1·8 mg (p<0·0001) reached the American Diabetes Association target HbA_{1c} of less than 7·0% (figure 3). The proportion of participants achieving these targets with liraglutide 1·8 mg was significantly higher than with liraglutide 1·2 mg.

Fasting plasma glucose concentrations (from laboratory values) fell during the first 2 weeks after randomisation in the liraglutide groups and 4 weeks in the glimepiride group and thereafter remained stable. At the end of the study, fasting plasma glucose concentrations were 8·65 mmol/L (SD 3·17), 8·25 mmol/L (2·75), and 9·27 mmol/L (2·99) in the liraglutide 1·2 mg, liraglutide 1·8 mg, and glimepiride groups, respectively. Decreases in fasting plasma glucose from baseline for the liraglutide groups were significantly greater than those in the glimepiride group (figure 4). A greater proportion of participants in the liraglutide groups achieved the American Diabetes Association fasting plasma glucose target (5·0–7·2 mmol/L) than in the glimepiride group (37·6% and 41·4% *vs* 22·2% for the liraglutide 1·2 mg and 1·8 mg *vs* glimepiride group, respectively, p≤0·0001 for each comparison).

Postprandial glucose concentrations, from self-monitored eight-point plasma-glucose profiles, decreased in all three treatment groups (figure 5).

HOMA-IR and fasting glucagon showed significant decreases with liraglutide but mean increases with glimepiride. Insulin resistance was reduced by 0·65 absolute percentage points in the liraglutide 1·2 mg group and 1·35% in the 1·8 mg group, but increased 0·85% in the glimepiride group (p=0·0249 and p=0·0011 for liraglutide 1·2 mg and 1·8 mg, respectively, *vs* glimepiride). The proinsulin to insulin ratio and HOMA-B showed no significant differences between treatments. Table 3 shows the ratios of proinsulin to insulin at baseline and end-of-study. These results suggest an improvement in insulin resistance, which could indicate either the effects of a GLP-1 agonist on the hyperglucagonaemia of type 2 diabetes or the limitations of HOMA methodology to assess B-cell function, or both.

Participants in the liraglutide groups lost weight whereas those taking glimepiride gained weight (figure 6). Weight loss in the first 16 weeks was sustained throughout the 52-week study. To determine if persistent nausea was a factor in weight loss, participants were analysed by the number of days they had nausea (>7 days or ≤7 days). Participants who had nausea for more than 7 days (29 on liraglutide 1·2 mg, 38 on liraglutide 1·8 mg, and nine on glimepiride) had a mean weight change of –3·24 kg, –3·39 kg, and –1·43 kg, compared with –1·85 kg, –2·26 kg, and +1·22 kg, respectively, for those with no nausea or up to 7 days of nausea (the differences were not significant for any treatment

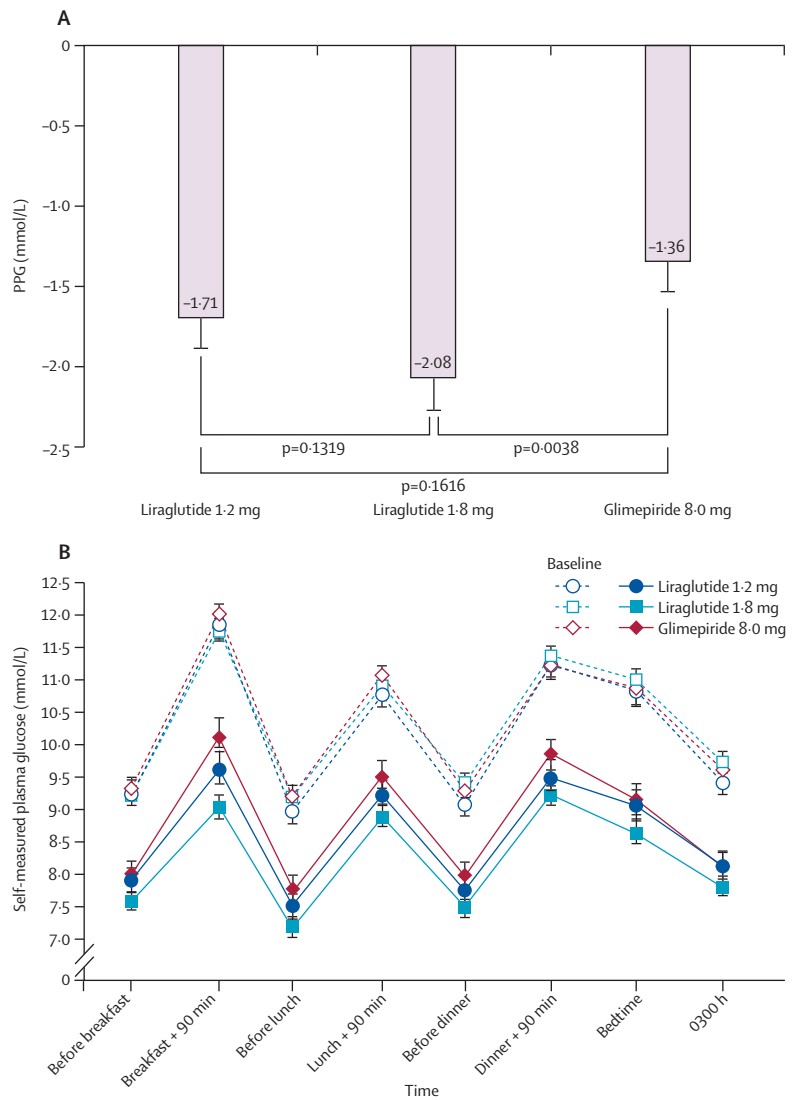

Figure 5: **Change in postprandial glucose**
Data from eight-point self-monitored plasma glucose (SMPG) values averaged for all three meals) from baseline to end-of-study with last observation carried forward (A); end-of-study eight-point SMPG (B). Data are mean (SE).

	Liraglutide 1·2 mg	Liraglutide 1·8 mg	Glimepiride 8 mg
Baseline	0·368 (0·231)	0·375 (0·223)	0·373 (0·376)
End-of-study	0·379 (0·398)	0·377 (0·292)	0·418 (0·242)

Data are mean (SD).

Table 3: **Proinsulin to insulin ratios**

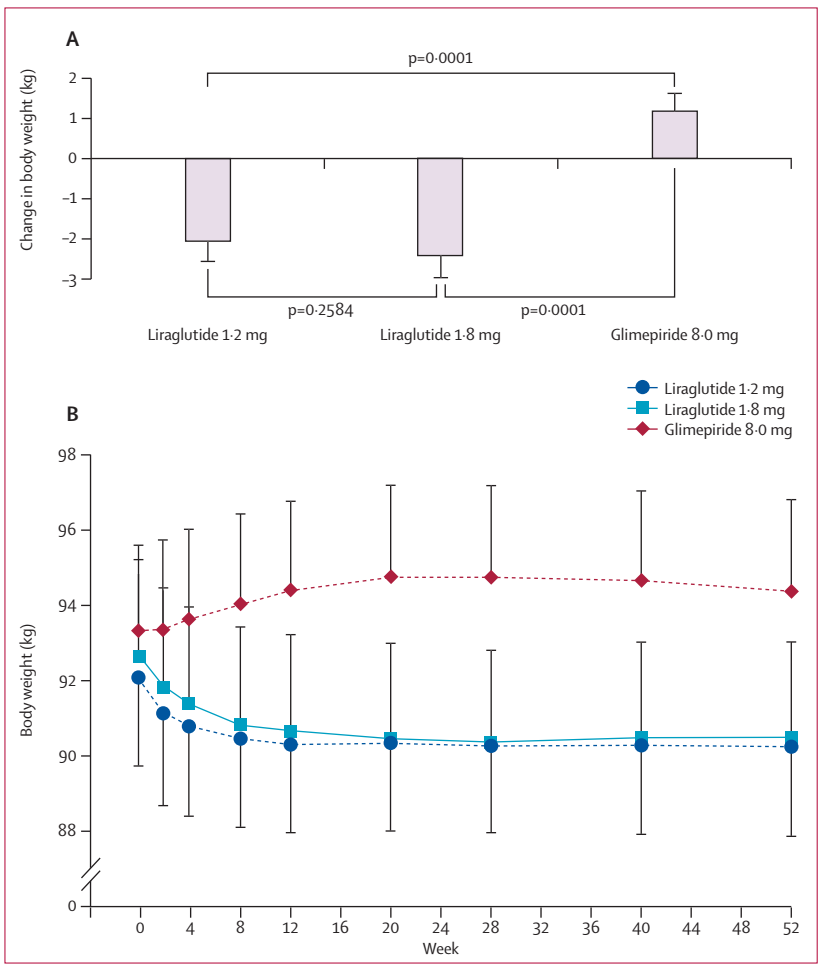

Figure 6: **Change in bodyweight**
Change from baseline to end-of-study with last observation carried forward (A) and change over time (B). Data are mean (SE).

group). Patients randomly assigned to liraglutide 1·8 mg reported improved quality of life scoring for physical and emotional domains compared with those assigned to glimepiride (p=0·02). These improvements seemed largely to result from improvements in weight image and weight concern (p<0·01). These results have been noted in a separate report of this study.[10]

Systolic blood pressure fell by 0·7 mm Hg (SD 13·7) in the glimepiride group compared with 2·1 mm Hg (SD 14·2) in the liraglutide 1·2 mg group (p=0·2912) and 3·6 mm Hg (14·1) in the liraglutide 1·8 mg group (p<0·0118). Mean diastolic blood pressure fell slightly but not significantly for all treatment groups.

No events of major hypoglycaemia (requiring third-party assistance) occurred; 12% and 8% of participants in the liraglutide 1·2 mg and 1·8 mg groups, respectively, had minor hypoglycaemia (plasma glucose <3·1 mmol/L), compared with 24% in the glimepiride group. The rate of minor hypoglycaemia was significantly lower (p<0·0001) for both liraglutide treatment groups (0·30 and 0·25 events per year for liraglutide 1·2 mg and 1·8 mg, respectively, compared with 1·96 events per year for glimepiride).

27·5% and 29·3% of participants in the liraglutide 1·2 mg and 1·8 mg groups, respectively, reported nausea, compared with 8·5% in the glimepiride group (p<0·0001 for both comparisons). Nausea generally occurred early during treatment and less than 10% of participants in the liraglutide 1·8 mg group had this side-effect by week 4. 9·3%, 12·4%, and 3·6% of participants in the liraglutide 1·2 mg and 1·8 mg, and glimepiride groups, respectively, reported vomiting (p<0·0001 for both comparisons with glimepiride). 8·9% in the glimepiride group reported diarrhoea compared with 15·5% and in the liraglutide 1·2 mg group (p=0·0283) and 18·7% in the liraglutide 1·8 mg group (p=0·0017). 11 (4%) of 251 and 6 (2%) of 246 participants taking liraglutide 1·2 mg and 1·8 mg, respectively, withdrew from the study because of vomiting, nausea, or diarrhoea, compared with none of 248 in the glimepiride group. Five participants in the 1·2 mg and one in the 1·8 mg groups withdrew specifically because of vomiting. Table 4 summarises all adverse events reported by more than 5% of participants.

Mean pulse rate increased by 3·2, 1·6, and 0·4 beats per min for liraglutide 1·2 mg and 1·8 mg, and glimepiride group, respectively (p=0·0027 and p=0·1422 for liraglutide 1·2 mg and 1·8 mg, respectively, *vs* glimepiride). After 52 weeks, calcitonin concentrations did not differ in participants taking liraglutide and those taking glimepiride.

Eight participants receiving liraglutide 1·8 mg had nine serious adverse events, 16 receiving liraglutide 1·2 mg had 18, and 13 receiving glimepiride had 17, including one death (an automobile accident classified as not related to treatment). Two participants had pancreatitis, one after 197 (liraglutide 1·2 mg) and another after 333 (liraglutide 1·8 mg) days of treatment. Both patients recovered; one continued in the study (1·2 mg). Despite confounding medical factors and the small number of events, a weak association between development of pancreatitis and treatment with liraglutide cannot be excluded.

Discussion

Treatment with liraglutide as monotherapy provided better glycaemic control for 52 weeks than did glimepiride, a traditional first-line secretagogue therapy for type 2 diabetes mellitus, in participants previously treated with either diet and exercise or oral antidiabetic monotherapy. Liraglutide improved glycaemic control with a low rate of hypoglycaemia.

Liraglutide led to decreases in both fasting and postprandial plasma glucose, and its 13 h half-life makes it suitable for once-daily use. Control of both fasting and postprandial plasma is needed for patients with type 2 diabetes mellitus to achieve HbA_{1c} goals.[11] Additionally, participants treated with liraglutide had significant weight loss and decreases in systolic blood

	Liraglutide 1·2 mg (n=251)		Liraglutide 1·8 mg (n=246)		Glimepiride 8 mg (n=248)	
	n (%)	Events	n (%)	Events	n (%)	Events
Gastrointestinal disorders	122 (49%)	282	126 (51%)	332	64 (26%)	139
Constipation	21 (8%)	24	258 (11%)	32	12 (5%)	12
Diarrhoea	39 (16%)	60	46 (19%)	61	22 (9%)	34
Flatulence	4 (2%)	4	13 (5%)	14	4 (2%)	4
Nausea	69 (27%)	91	72 (29%)	107	21 (8%)	28
Vomiting	31 (12%)	35	23 (9%)	32	9 (4%)	10
General disorders and administration site conditions	33 (13%)	41	41 (17%)	59	37 (15%)	44
Infections and infestations	119 (47%)	207	102 (41%)	184	90 (36%)	153
Influenza	17 (7%)	20	20 (8%)	25	9 (4%)	15
Nasopharyngitis	17 (7%)	18	9 (4%)	10	13 (5%)	14
Sinusitis	15 (6%)	16	13 (5%)	18	15 (6%)	17
Upper respiratory tract infection	23 (9%)	28	24 (10%)	30	14 (6%)	21
Urinary tract infection	20 (8%)	24	10 (4%)	13	10 (4%)	11
Injury, poisoning, and procedural complications	22 (9%)	26	24 (10%)	27	29 (12%)	33
Investigations	16 (6%)	21	23 (9%)	28	18 (7%)	24
Metabolism and nutrition disorders	38 (15%)	46	35 (14%)	42	28 (11%)	30
Musculoskeletal and connective tissue disorders	48 (19%)	63	46 (19%)	59	38 (15%)	55
Back pain	14 (6%)	16	11 (5%)	11	11 (4%)	11
Nervous system disorders	56 (22%)	101	49 (20%)	71	55 (22%)	78
Dizziness	13 (5%)	18	16 (6%)	18	13 (5%)	14
Headache	27 (11%)	47	18 (7%)	25	23 (9%)	30
Psychiatric disorders	21 (8%)	25	21 (9%)	21	14 (5%)	17
Respiratory, thoracic, and mediastinal disorders	21 (8%)	31	28 (11%)	39	28 (11%)	35
Skin and subcutaneous tissue disorders	23 (9%)	26	24 (10%)	26	17 (7%)	19
Vascular disorders	11 (4%)	12	15 (6%)	15	17 (7%)	21
Hypertension	7 (3%)	7	8 (3%)	8	15 (6%)	17

A treatment-emergent adverse event is defined as an event occurring between first and last dose +7 days or starting before first dose with increasing severity during treatment.

Table 4: **Treatment-emergent adverse events reported by more than 5% of participants, by system organ class and preferred term**

pressure. The additional benefit of weight loss early in the course of treatment might have long-term effects as shown in the UKPDS[2] and Look AHEAD[12] studies.

Exenatide, another GLP-1 receptor agonist, is a synthetic exendin-4, with a half-life of 2·4 h, requiring twice daily administration before meals. A recent 24-week study[13] of patients naive to oral antidiabetic treatment who initiated exenatide therapy reported reductions in HbA_{1c} of 0·7% and 0·9% with 5 μg and 10 μg, twice daily, respectively. Fasting serum glucose declined by 1·0 mmol/L for both groups, and bodyweight decreased by 2·8 kg and 3·1 kg, respectively. Two previously published 30-week studies of exenatide added to previous monotherapy (4 mg glimepiride[14] or 1500 mg metformin[15]) reported decreases in HbA_{1c} of 0·4–0·9% and weight loss of 0·9–1·6 kg (+sulphonylurea), and 1·6–2·8 kg (+metformin). Fasting plasma glucose decreased by 0·3–0·6 mmol/L, with significant reductions in postprandial plasma glucose as shown by a standardised meal-tolerance test in the study with metformin.

The oral antidiabetic sitagliptin is an inhibitor of dipeptidyl peptidase 4 given once daily. In a 24-week study of patients naive to oral antidiabetic drugs,[16] sitagliptin reduced HbA_{1c} by 0·79% and 0·94% (sitagliptin doses of 100 mg and 200 mg, respectively) and fasting plasma glucose by 1·0 mmol/L and 1·2 mmol/L. Unlike GLP-1 receptor agonists, such as liraglutide and exenatide, sitagliptin did not lead to weight change.

Traditional first-line therapy might not be appropriate for all patients. Metformin is poorly tolerated by about 5% of patients[17] and is contraindicated for renal reasons, which affect almost 30% of patients within 15 years of diagnosis of type 2 diabetes mellitus.[18] Exenatide and sitagliptin require dose adjustments in patients with renal impairment,[19,20] and exenatide is contraindicated in patients with severe renal impairment. A recent pharmacokinetic study of liraglutide reported no need for dose adjustment when comparing healthy participants with those with severe renal impairment.[21]

Similar concerns are evident for other treatments. In the ADOPT (A Diabetes Outcome Progression Trial) study,[1] glibenclamide treatment produced a 39% incidence of hypoglycaemia and had a higher dropout rate than other therapies (44% *vs* 37% for rosiglitazone and 38% for metformin), despite having the greatest initial reductions

in HbA_{1c} and fasting plasma glucose after 6 months of treatment. Durability during the 5-year study was not seen with glibenclamide; and HbA_{1c} control, as indicated by the Kaplan-Meier cumulative incidence, failed in 34% of patients after 5 years (compared with 21% of those given metformin). The 4-year extension of the LEAD-3 study, as well as other continuing long-term studies of liraglutide, will help us assess the durability of liraglutide treatment and identify subpopulations that best respond to liraglutide treatment.

Liraglutide treatment as initial monotherapy is a safe and effective option for treatment for patients with type 2 diabetes early in the course of disease. Improvement in key efficacy endpoints, such as HbA_{1c}, fasting plasma glucose, and blood pressure happen quickly after initiation of liraglutide treatment. With liraglutide 1·8 mg, the decrease in HbA_{1c} and weight remained stable through the 52 weeks for patients who had not had antidiabetic drugs. Because of the low rate of hypoglycaemia with liraglutide monotherapy, there is no greater need for glucose monitoring for safety concerns than with other treatments. The increased insulin secretion with liraglutide, being glucose-dependent, retains more physiological stimulus-secretion coupling between glucose and insulin than does a sulphonylurea that acts by potassium-channel closure and produces more hypoglycaemia than does a GLP-1 agonist. However, type 2 diabetes is characterised by progressive B-cell failure leading to insulin deficiency, therefore whether the effects obtained by this GLP-1 analogue would be as robust in later stages of disease is unclear.

Additional weaknesses and biases of this study include the selection bias of patients who volunteer for a study, especially for one involving an injectable drug. Also, investigator enthusiasm for this drug might have resulted in an artificially low drop-out rate, as compared with rates seen in routine general practice after approval. The data from this study cannot be extrapolated to very young and very old people since both groups were excluded from the trial.

Liraglutide was well tolerated although gastrointestinal adverse events were generally higher with liraglutide than with glimepiride. However, these events were mostly transient and most patients who withdrew because of gastrointestinal adverse events did so within the first 4 weeks of the study. In the exenatide trials cited above, 36–51% of participants reported nausea and 10–13% reported vomiting with exenatide treatment. Appearance of antibodies to liraglutide is not reported as the trial extension is in progress and accurate antibody assessment cannot be made while participants have liraglutide in their plasma. Other studies with liraglutide reported a very low prevalence of antibodies.

On the basis of these results, we conclude that liraglutide is safe and effective as initial pharmacological therapy for type 2 diabetes mellitus and has advantages over other drugs used in monotherapy, such as greater reductions in weight, the number of hypoglycaemic events, and systolic blood pressure.

Contributors

AG, PMH, and MZ participated in the concept and design of the study. AG, RH, RR, PMH, and MZ participated in the interpretation of data and revision of the paper. AG, RH, RR, PAG-H, HR-P, IO-A, and BB were major contributors of clinical data and contributed patients. All authors contributed to the report.

LEAD-3 Study Investigators

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Conflict of interest statement

Liraglutide is a Novo Nordisk proprietary compound under development. AG has attended speakers' bureau, is an advisory board member, and has received research grants from Novo Nordisk. RH has attended speakers' bureau, been a consultant for, and received research grants from, Novo Nordisk. RR is an advisory board member and has received research grants from Novo Nordisk. MZ and PMH are employed by Novo Nordisk. MZ owns stock in Novo Nordisk. BB has attended speakers' bureau, acted as a consultant for, and received research grants from, Novo Nordisk. PAG-H, HR-P, and IO-A have no conflict of interest to declare.

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