



# 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<sub>1c</sub>). Analysis was done by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NCT00294723.

**Findings** At 52 weeks, HbA<sub>1c</sub> 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<sub>1c</sub>, weight, hypoglycaemia, and blood pressure than does glimepiride.

**Funding** Novo Nordisk A/S.

## Introduction

Type 2 diabetes mellitus is a progressive disease; many treatments work early in the course of disease but do not remain effective.<sup>1,2</sup> Glucagon-like peptide 1 (GLP-1) stimulates glucose-dependent insulin secretion, suppresses glucagon secretion, and moderates appetite by delaying gastric emptying and reducing hunger.<sup>3</sup> Endogenous GLP-1 has a very short half-life (1.5 min) because of rapid degradation by dipeptidyl peptidase 4,<sup>3</sup> which restricts its therapeutic usefulness. Liraglutide is an analogue of human GLP-1 with 97% homology to the endogenous protein<sup>4</sup> and a half life of 13 h, which gives it a pharmacokinetic profile suitable for once daily treatment.<sup>5</sup>

Liraglutide restores glucose-dependent insulin secretion after one injection in patients with type 2 diabetes mellitus.<sup>6</sup> In a 14 week monotherapy trial,<sup>7</sup> treatment with liraglutide produced substantial and clinically significant reductions in fasting and postprandial glucose concentrations and glycosylated haemoglobin (HbA<sub>1c</sub>), 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-naïve, 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/m<sup>2</sup> 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,  $\alpha$ -glucosidase inhibitors, and thiazolidinediones (1500 mg metformin or 30 mg pioglitazone were allowed) for at least 2 months. Patients had a screening HbA<sub>1c</sub> 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 corticosteroids, hypoglycaemia unawareness or recurrent severe hypoglycaemia, and impaired liver function (aspartate aminotransferase or alanine aminotransferase concentrations  $\geq 2.5$  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<sup>8</sup> and

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Good Clinical Practice guidelines.<sup>9</sup> This trial is registered with ClinicalTrials.gov, number NCT00294723.

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.

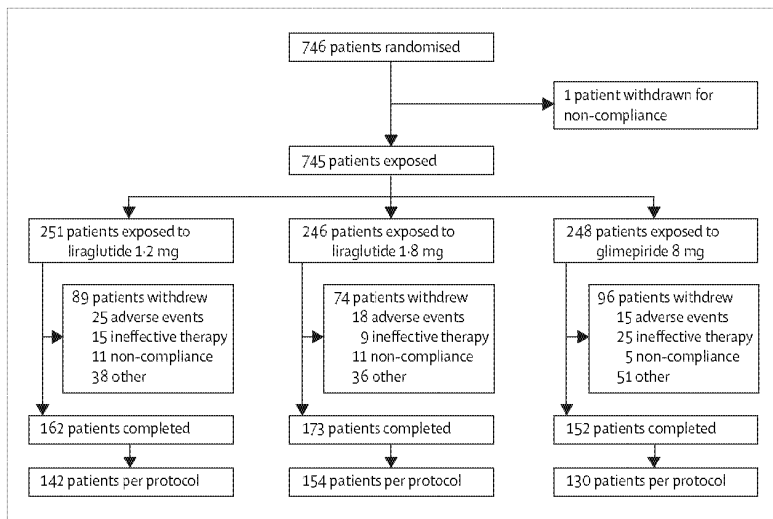
Randomisation was done with telephone-based or web-based systems. Participants were randomly assigned to the lowest available number. Recruitment began on Feb 7, 2006, with the last patient visit for this portion of the study on Nov 7, 2007. Participants completing the study could enrol, subject to eligibility,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

The primary outcome was change in value of HbA<sub>1c</sub> 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<sub>1c</sub>, (SD of 1.2% and a two-sample one-sided  $\alpha$  of 0.025). With the assumption of a 30% drop-out rate, we enrolled



**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/m <sup>2</sup> )	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 <sub>1c</sub> (%)	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

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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> in the liraglutide treatment groups were significantly greater than those in the glimepiride group, as shown by the differences

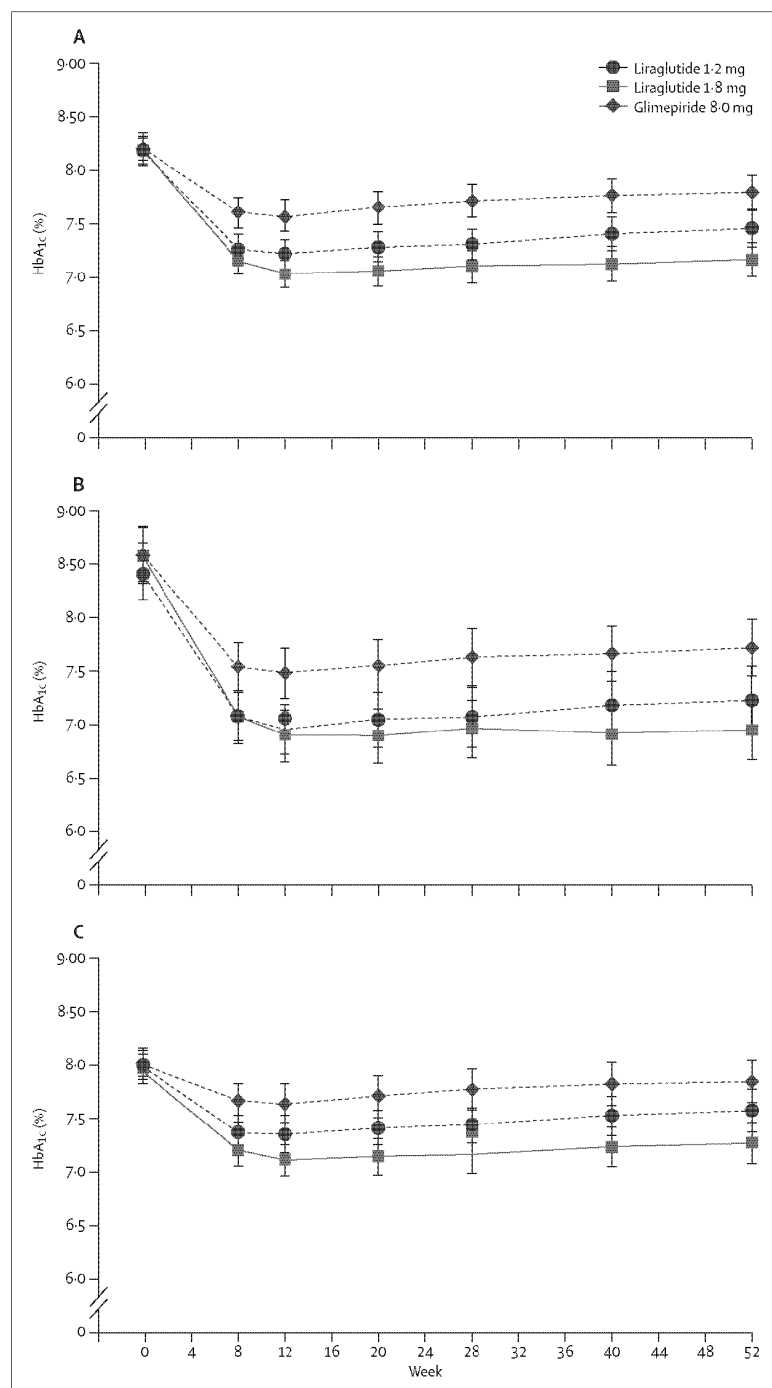


Figure 2: Efficacy of glycaemic control shown by HbA<sub>1c</sub> profiles

(A) all participants. (B) drug-naive participants. (C) participants previously treated with one oral antidiabetic drug. Data are mean (SE).

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

greater than that with liraglutide 1.2 mg (-0.29%; -0.50 to -0.09,  $p=0.0046$ ).

Figure 2 shows mean HbA<sub>1c</sub> values over time for all participants (all points after baseline with last observation carried forward) and for those previously treated with diet

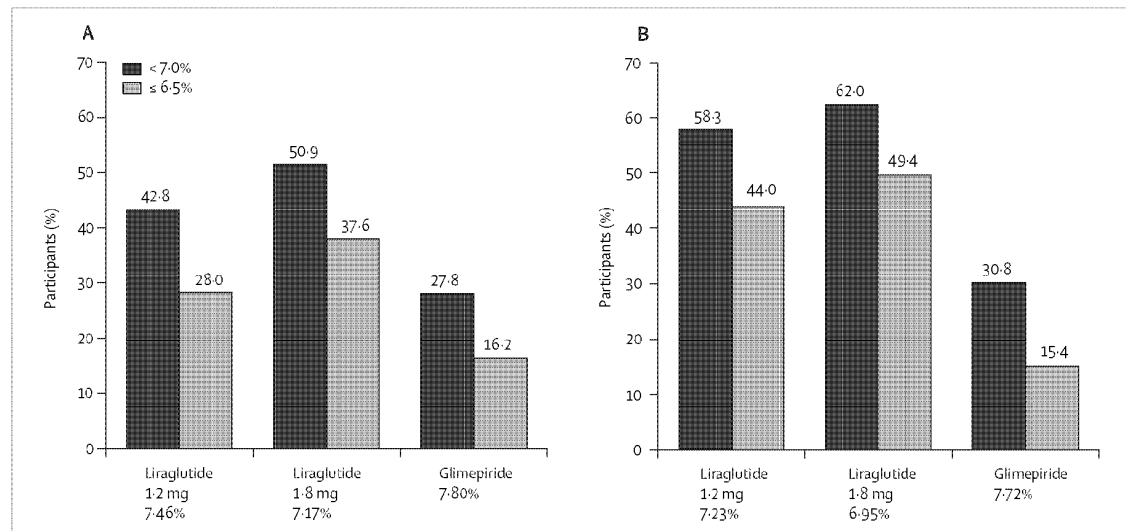
	Diet and exercise	Oral antidiabetic monotherapy
Liraglutide 1.2 mg	-1.19% (0.15)*	-0.47% (0.10)†
Liraglutide 1.8 mg	-1.60% (0.15)‡	-0.71% (0.09)‡
Glimepiride	-0.88% (0.13)	-0.17% (0.08)

Data are mean (SE). Compared with change with glimepiride \* $p=0.0234$ , † $p=0.0215$ , and ‡ $p<0.0001$ .

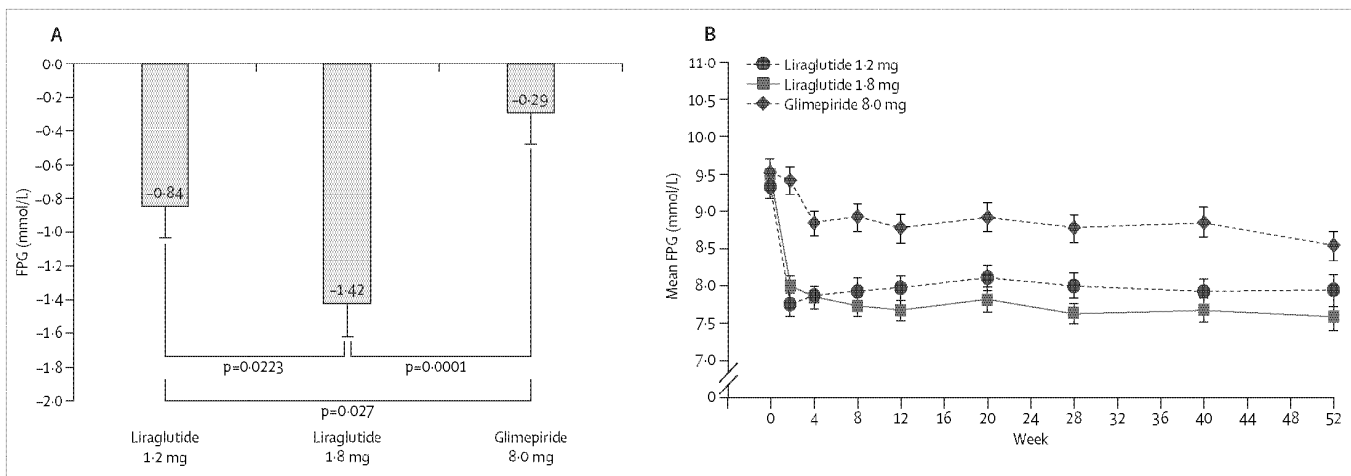
**Table 2: Decreases in HbA<sub>1c</sub> at 52 weeks for each trial intervention by previous treatment**

and exercise or monotherapy. HbA<sub>1c</sub> values generally decline over the first 8–12 weeks of treatment. From week 12 to week 52, HbA<sub>1c</sub> values increased slightly but significantly for participants treated with liraglutide 1.2 mg ( $p=0.0071$ ) and glimepiride ( $p=0.0006$ ); however, HbA<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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/



**Figure 3: Participants achieving HbA<sub>1c</sub> 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<sub>1c</sub> 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).

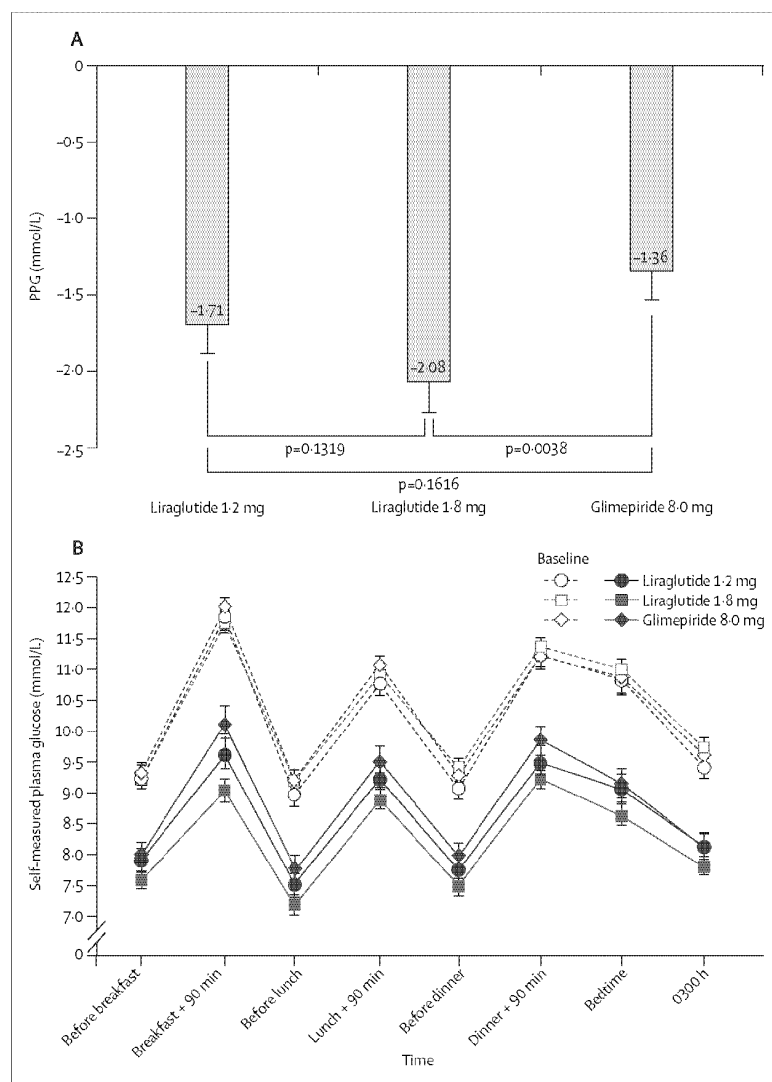
American Association of Clinical Endocrinologists target HbA<sub>1c</sub> of 6.5% or less, compared with 16% in those on glimepiride ( $p=0.0025$  and  $p<0.0001$  for liraglutide 1.2 mg and 1.8 mg, respectively; figure 3). Although participants previously treated with diet and exercise had higher baseline HbA<sub>1c</sub> values, a greater proportion achieved the HbA<sub>1c</sub> 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<sub>1c</sub> 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,  $p\leq 0.0001$  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



**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).

or  $\leq 7$  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

	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**

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