CME SERIES: VOL. 6

article insights™

A nutshell analysis of medical journal articles for family physicians

volume 6

Managing the Patient with Type 2 Diabetes When Lifestyle Intervention and Metformin Don't Achieve the Target Glycemic Goal

PCMG
Primary Care Metabolic Group

Primary Care Education Consortium

about article insights™

Article Insights™ CME Series are educational activities that provide practical pearls to the primary care physician (PCP) on various therapeutic areas treated and managed by PCPs. Each activity includes a reprint of an article that has recently been published in a specialty journal as well as a Question and Answer interview between two PCPs on the important "take-away" points of the article reprint.

In this edition of **Article Insights™ CME Series**, Dr. Brunton will interview Dr. Wender on how PCPs may apply the findings in the journal article, "Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial" by Alan Garber, MD et al, to better manage diabetes in their patients.

faculty

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learning objectives

After reviewing this activity, the reader will be better able to:

1. List the preferred treatment options as recommended by the American Diabetes Association/European Association for the Study of Diabetes consensus panel for patients with type 2 diabetes mellitus who have not achieved target glycemic goals with lifestyle modification and titrated metformin therapy.
2. Compare the efficacy and safety of liraglutide and glimepiride in the population included and the doses used in the study by Garber et al.
3. Relate the results of the study by Garber et al with the ADA/EASD consensus panel recommendations.

target audience

Primary care physicians and clinicians who have an interest in treating patients with diabetes.

Sponsor Disclosure Statement

As a continuing medical education provider accredited by the ACCME, it is policy of PCEC to require any individual in a position to influence educational content to disclose the existence of any financial interest or other personal relationship with the manufacturer(s) of any commercial product(s).

PCEC clinical staff have provided financial disclosure and have no conflicts of interest to resolve related to this activity.

The medical accuracy reviewer for this activity, Joseph Tibaldi, MD, disclosed he is on the advisory board and speakers' bureau for Novo Nordisk Inc.

The CME reviewer for this activity, Allan Wilke, MD have no real or apparent conflicts of interest to report.

Faculty Disclosure Statements

Dr. Brunton disclosed he is on the advisory boards for Amylin, Abbott Laboratories, Novo Nordisk Inc., and Takeda Pharmaceuticals.

Dr. Wender disclosed he is a medical and scientific advisory board member for Genenews and Epigenomics.

Conflict of Interest Statement

When individuals in a position to control content have reported financial relationships with one or more commercial interests, PCEC works with them to resolve such conflicts to ensure that the content presented is free of commercial bias. The content of this publication was vetted by the following mechanisms and modified as required to meet this standard:

- Content peer-review by an external topic expert
- Content peer-review by an external CME reviewer
- Content validation by internal PCEC clinical editorial staff

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In accordance with ACCME guidelines, the faculty has been asked to disclose discussion on unlabeled or unapproved uses of drugs or devices during the course of their interview.

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Accreditation begins on: May 1, 2009 and ends on: May 1, 2010.

This activity has been reviewed and is acceptable for up to 2 Prescribed credits by the American Academy of Family Physicians. Of these credits, 1 conforms to the AAFP criteria for evidence-based CME clinical content. CME credit has been increased to reflect 2 for 1 credit for only the EB CME portion. AAFP accreditation begins May 1, 2009. The term of approval is for one year from this date, with option for yearly renewal. When reporting AAFP credit, report total Prescribed and Elective credit for this activity. It is not necessary to label credit as evidence-based for reporting purposes.

EB CME AAFP Evidence-Based CME

The EB CME credit awarded for this activity was based on practice recommendations that were the most current with the strongest level of evidence available at the time this activity was approved. Since clinical research is ongoing, AAFP recommends that learners verify sources and review these and other recommendations prior to implementation into practice.

Clinical Practice Recommendations for AAFP EB CME Designation

Practice Recommendation #1: Metformin therapy should be initiated concurrently with lifestyle intervention at diagnosis.

Evidence-Based Source: Diabetes Care

Supporting Evidence: Page 8 from: Nathan DM, et al for the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2008;31(12):1-11.

Strength of Evidence: The consensus panel utilized 2 sources: 1) evidence-based review of a wide variety of studies related to the use of drugs as monotherapy or in combination to lower glycemia; 2) clinical judgment, that is, their collective knowledge and clinical experience, which takes into account benefits, risks, and costs in the treatment of diabetes.

Practice Recommendation #2: If lifestyle intervention and the maximal tolerated dose of metformin fail to achieve or sustain the glycemic goals, another medication should be added within 2–3 months of the initiation of therapy or at any time when the target A1C level is not achieved.

Evidence-Based Source: Diabetes Care

Supporting Evidence: Page 8 from: Nathan DM, et al for the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2008;31(12):1-11.

Strength of Evidence: The consensus panel utilized 2 sources: 1) evidence-based review of a wide variety of studies related to the use of drugs as monotherapy or in combination to lower glycemia; 2) clinical judgment, that is, their collective knowledge and clinical experience, which takes into account benefits, risks, and costs in the treatment of diabetes.

Practice Recommendation #3: When hypoglycemia is particularly undesirable (e.g., in patients who have hazardous jobs), the addition of exenatide or pioglitazone may be considered. Rosiglitazone is not recommended. If promotion of weight loss is a major consideration and the A1C level is close to target (<8.0%), exenatide is an option.

Evidence-Based Source: Diabetes Care

Supporting Evidence: Page 8 from: Nathan DM, et al for the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2008;31(12):1-11.

Strength of Evidence: The consensus panel utilized 2 sources: 1) evidence-based review of a wide variety of studies related to the use of drugs as monotherapy or in combination to lower glycemia; 2) clinical judgment, that is, their collective knowledge and clinical experience, which takes into account benefits, risks, and costs in the treatment of diabetes.

Medium

Text publication in the form of a reprint article with a corresponding question and answer analysis by physicians.

Statement of Support

This program is sponsored by the Primary Care Education Consortium and Primary Care Metabolic Group and is supported by an educational grant from Novo Nordisk Inc.

Method of Physician Participation

To receive CME credit, please read the question and answer interview **as well as** the enclosed article reprint. Upon completion, go to: **www.pceconsortium.org/article6** to complete the online post-test and evaluation to receive your certificate of completion. **Please note:** it is not required that you obtain a certain score on the post-test in order to receive credit.

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

*Alan Garber, Robert Henry, Robert Ratner, Pedro A Garcia-Hernandez, Hiromi Rodriguez-Pattzi, Israel Olvera-Alvarez, Paula M Hale, Milan Zdravkovic, Bruce Bode, for the LEAD-3 (Mono) Study Group**

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.**

Funding **Novo Nordisk A/S.**

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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.

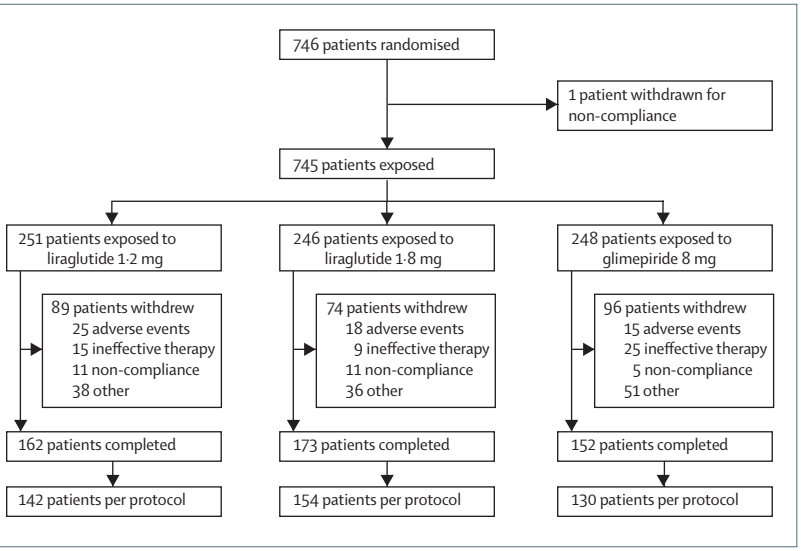

Figure 1: **Trial profile**
Analyses were done on the intention-to-treat population exposed to at least one dose of treatment. *Patient withdrawn from liraglutide 1·8 mg group before exposure.

	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

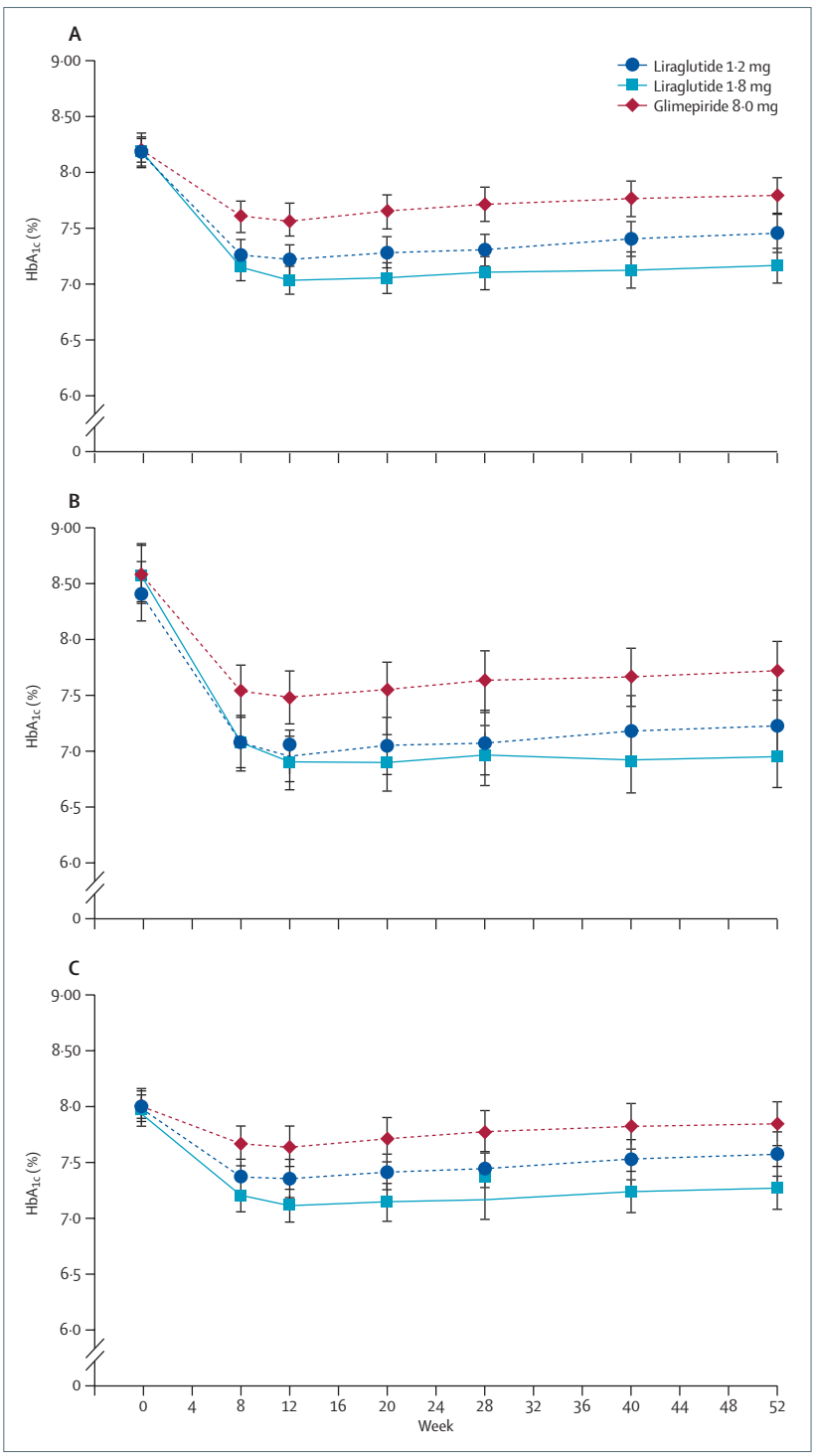

Figure 2: **Efficacy of glycaemic control shown by HbA_{1c} profiles**
(A) all particpants. (B) drug-naive participants. (C) participants previously treated with one oral antidiabetic drug. Data are mean (SE).

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**

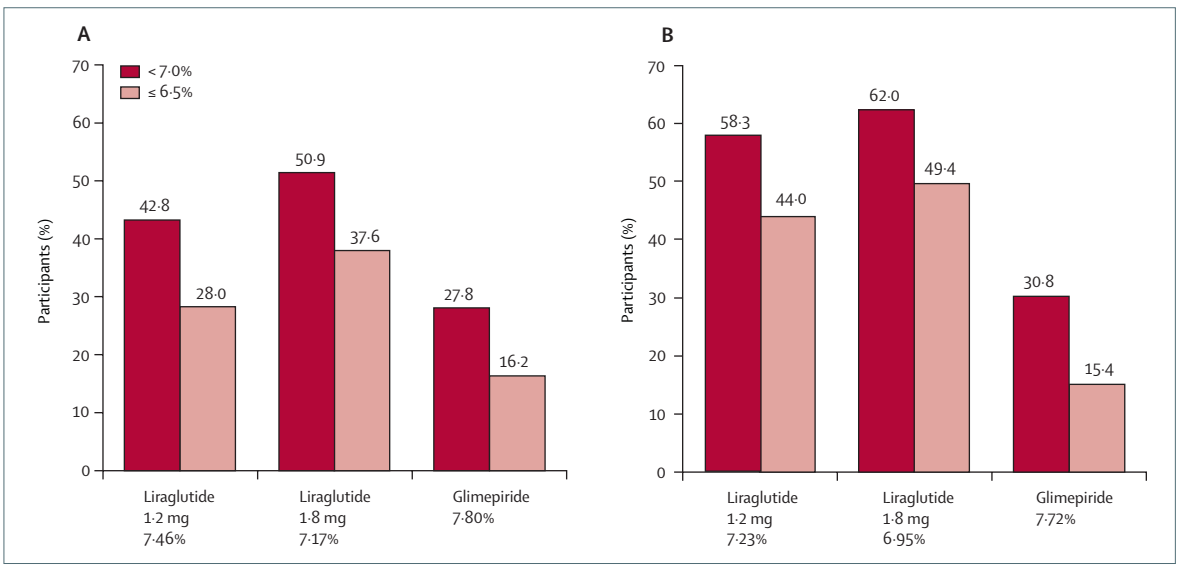

***Figure 3*: Participants achieving HbA_{1c} targets of less than 7·0% (ADA) and less than or equal to 6·5% (IDF/AACE)**
(A) all participants. (B) drug-naive participants. Percentages under each treatment group are mean final HbA_{1c} values.

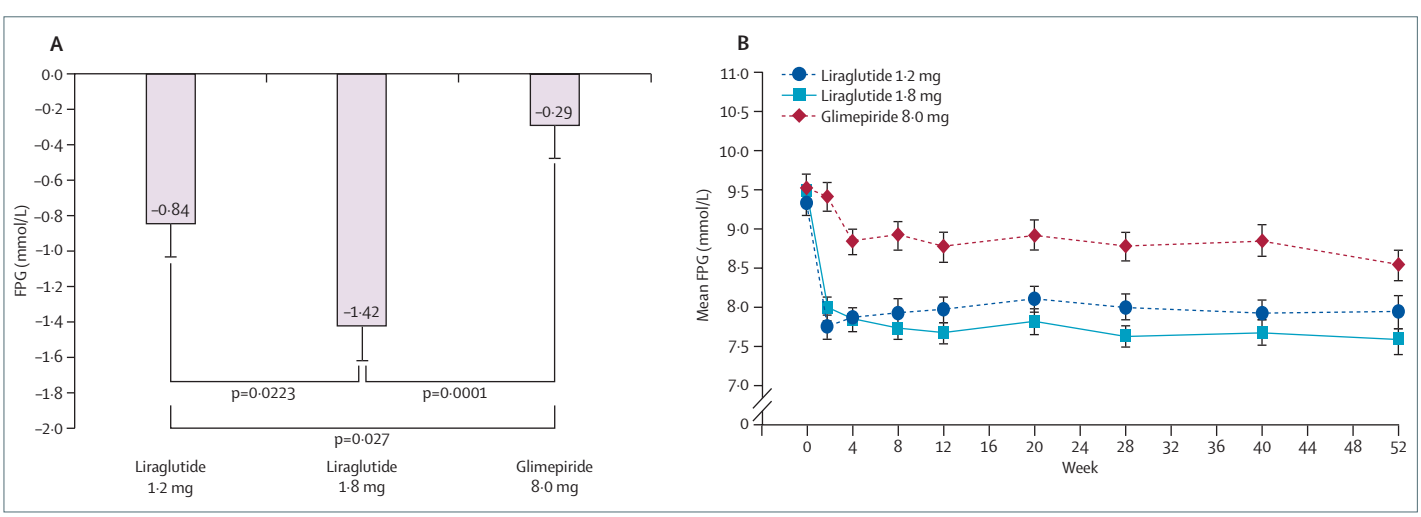

***Figure 4*: Change in fasting plasma glucose (FPG)**
Data from laboratory values: difference from baseline to end-of-study with last observation carried forward (A) and change over time (B). Data are mean (SE).

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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

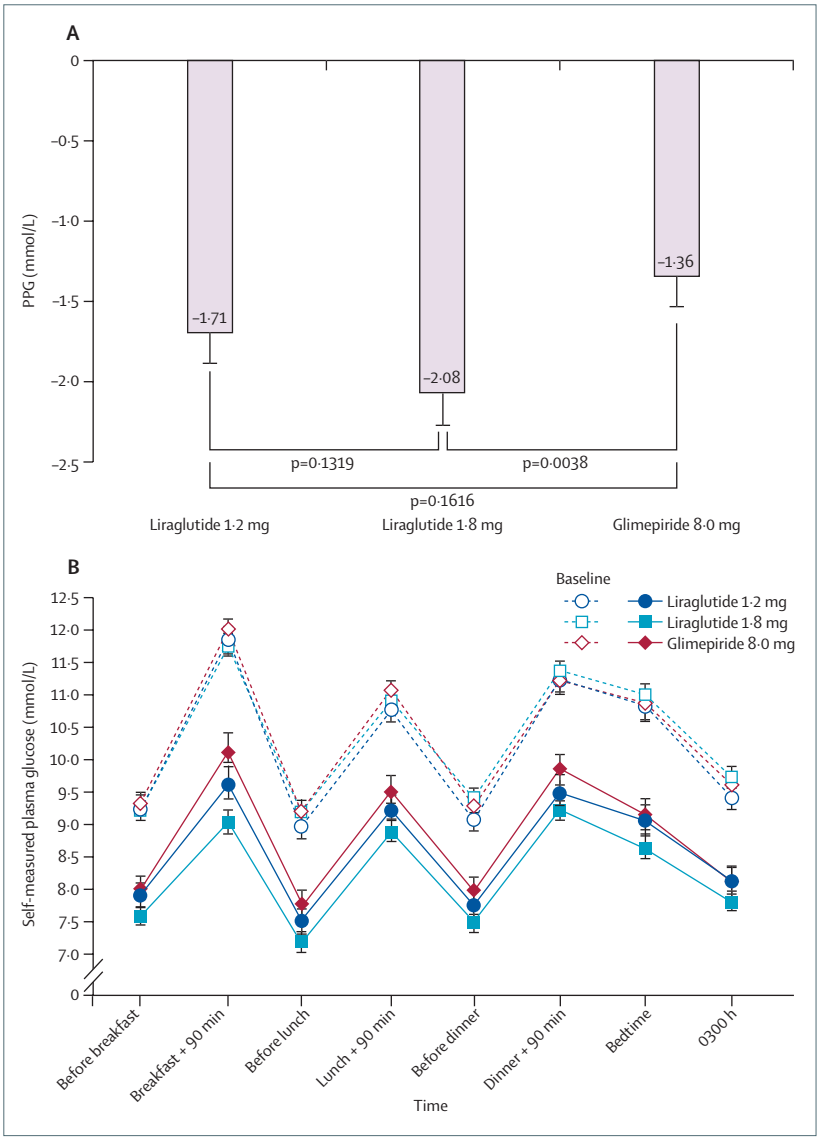

Figure 5: **Change in postprandial glucose**
Data from eight-point self-monitored plasma glucose (SMPG) values averaged for all three meals) from baseline to end-of-study with last observation carried forward (A); end-of-study eight-point SMPG (B). Data are mean (SE).

	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**

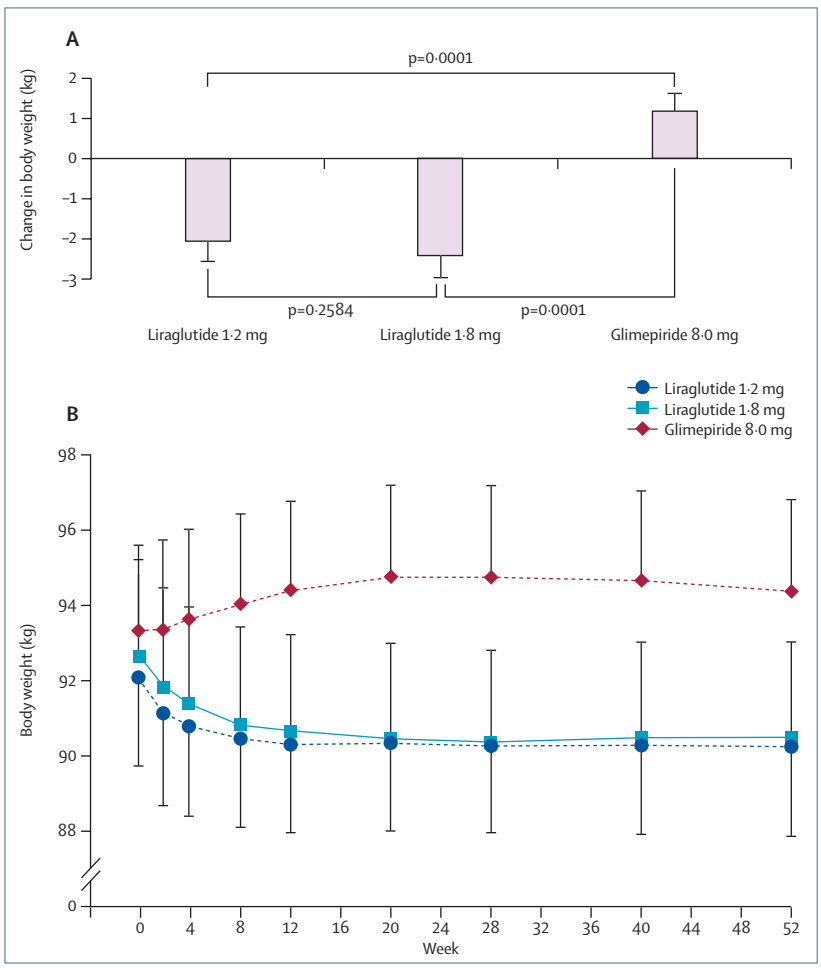

Figure 6: **Change in bodyweight**
Change from baseline to end-of-study with last observation carried forward (A) and change over time (B). Data are mean (SE).

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

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	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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article insights™ q&a

CME Series: volume 6

Managing the Patient with Type 2 Diabetes When Lifestyle Intervention and Metformin Don't Achieve the Target Glycemic Goal

In this sixth issue of Article Insights, Richard C. Wender, MD, expands on the article by Garber et al to focus on the primary care management of a patient with type 2 diabetes mellitus who does not have an A1C level below the target level of 7%.

Question 1

Dr. Brunton: The combination of lifestyle intervention and metformin is routinely used in the primary care setting as initial therapy for patients with type 2 diabetes mellitus (T2DM). A common challenge we face is when and how to modify therapy. Let's talk first about when to modify therapy.

Dr. Wender: First, it's important to emphasize that initiating a combination of lifestyle intervention and metformin at the time of diagnosis is now recommended by the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) (1) rather than adding metformin after lifestyle intervention fails. This recommendation by the panel underpins the overall more aggressive "treat-to-success" approach rather than the "treat-to-failure" approach largely because of the generally progressive nature of T2DM and the associated decline of pancreatic beta cell function. Consistent with this "treat-to-success" approach, the panel advised that interventions must be changed at as rapid a pace as titration of medications allows when target glycemic goals are not being achieved.

Question 2

Dr. Brunton: What specific recommendations does the panel provide about titrating metformin?

Dr. Wender: The panel recommends that metformin should be titrated over 1-2 months to its maximally effective dose of 850-1000 mg twice daily. As we know, not all patients are able to tolerate this dose. The importance of titrating to the maximum tolerated dose and getting to this dose as quickly as possible can't be overemphasized.

If the combination of lifestyle intervention and maximal tolerated doses of metformin does not achieve the target glycemic goal within 2-3 months of the initiation of therapy, or at any time thereafter, the addition of a second medication is warranted. This recommendation emerges from consideration of the evidence suggesting that aggressive lowering of blood glucose in patients newly diagnosed with T2DM can result in normoglycemia and may reduce the need for additional glucose-lowering medications.

Question 3

Dr. Brunton: So for the vast majority of patients with T2DM, that means that if the A1C level is 7% or above despite maximal management with lifestyle intervention and metformin, a second medication should be added at that point. Is that correct?

Dr. Wender: Yes. Allowing the A1C level to be at 7.0% or above for months is not acceptable for the vast majority of patients with T2DM because of the established benefits with an A1C level less than 7%. And we know that using a combination of two medications from different groups is generally more effective than a high dose of one drug.

Recent published studies from the ACCORD trial (2) and Veterans Administration Diabetes Trial (VADT) (3), are forcing us to re-think how we define the most appropriate A1C goal for each individual and challenge the concept that lower A1C levels are appropriate for everyone. But when reviewing all available data, generally speaking, a goal of an A1C less than 7% is best for most patients. So our goal for most patients is to rapidly achieve an A1C level of less than 7% and to then help the patient maintain that level over the remainder of her/his lifetime. Again, we want to treat-to-success.

Question 4

Dr. Brunton: Given the growing number of treatment options, which of these should be added to metformin?

Dr. Wender: First, it's important to emphasize that along with progression of therapy, lifestyle interventions should be continued and, with continued education, intensified if possible. We don't want patients to believe that addition of new therapies minimizes or negates the need for emphasis on dietary improvements and increased activity.

I think it's particularly gratifying to know that we now have a menu of options that enable us to address the known pathophysiologic mechanisms of T2DM. Clearly, all of the agents available to lower the blood glucose are effective, although with varying degrees and speed. The ADA/EASD panel recommends two tiers of preferred therapies. First-tier add-on therapies include insulin or a sulfonylurea, as they are the best established, most effective, and cost effective in achieving the target glycemic goals. Two second-tier options for advancing first-step lifestyle/metformin therapy include either a thiazolidinedione or glucagon-like peptide 1 (GLP-1) receptor agonist. These are listed second because the evidence is not as extensive and they are relatively more expensive. The thiazolidinediones have been used for many years and are effective in lowering blood glucose. However, side effects are problematic in some patients. The GLP-1 receptor agonists are effective in lowering blood glucose and offer some important benefits; however, it is important to recognize they have been available for only a short time, so there is both less experience and fewer long-term trials utilizing GLP-1 receptor agonists.

The remainder of the medications available to lower blood glucose—the alpha-glucosidase inhibitors, glinides, pramlintide, and dipeptidyl peptidase-4 inhibitors—are placed in a third group by the panel. In addition to lower or equivalent effectiveness to the preferred therapies in lowering blood glucose, the clinical data regarding their use is often limited and many are relatively more expensive. The panel was less specific about the use of the medications in this group, although each has a niche in primary care.

Question 5

Dr. Brunton: So either insulin or a sulfonylurea would be two of the preferred choices to add to lifestyle intervention and metformin if the patient's A1C goals are not met?

Dr. Wender: Insulin would be preferred as the second medication if the A1C is > 8.5% or if the patient has symptoms secondary to hyperglycemia. The combination of metformin and insulin is a particularly effective means of lowering blood glucose, while limiting weight gain, which can be a concern when insulin is used alone. Intermediate- or long-acting basal insulin is recommended as initial insulin therapy. Of course, physician and patient barriers, such as needle phobia, risk of hypoglycemia, and clinical inertia must be addressed to successfully use insulin.

Sulfonylureas are effective in lowering glycemia, are easy to use and inexpensive, and act by a mechanism different from metformin, making them a reasonable choice in patients whose A1C is under 8% or so. Hypoglycemia and weight gain can be a problem. Given the panel's treat-to-success approach, the addition of a sulfonylurea would typically occur within a few months of diagnosis. A sulfonylurea or other secretagogue should be discontinued at the time insulin is added since their actions are not considered synergistic.

Question 6

Dr. Brunton: What role do the thiazolidinediones and GLP-1 receptor agonists play in the progression of therapy for type 2 diabetes?

Dr. Wender: As second-tier therapies and as alternatives to first-tier insulin or a sulfonylurea, the panel recommends their use in specific clinical settings. Either a thiazolidinedione or GLP-1 receptor agonist may be added to lifestyle and metformin, and for many patients would be preferred to the agents in the third group of glucose-lowering medications. When the risk of hypoglycemia is particularly undesirable (e.g., patient in a hazardous job), the GLP-1 receptor agonist exenatide or the thiazolidinedione pioglitazone but not rosiglitazone due to cardiovascular concerns can be considered instead of insulin or a sulfonylurea. If promotion of weight loss

is a major consideration and the A1C is less than 8%, exenatide may be the preferred option. Given that many patients with T2DM are overweight, the ability of exenatide to promote weight loss is an important benefit and differentiates it from many of the other medications for T2DM, including insulin. Although significant weight loss is not achieved by all patients, I've found that the weight loss potential with exenatide helps to improve adherence to therapy, as patients are motivated by this added benefit.

Question 7

Dr. Brunton: Given that the GLP-1 receptor agonists were only briefly mentioned in the 2008 ADA diabetes management guidelines (4), their inclusion as a preferred therapy option in the ADA/EASD consensus guidelines would seem to indicate we've learned a lot about this group of drugs in a short period of time.

Dr. Wender: I agree. Exenatide has been available in the US since 2005 and nearly 50 clinical trials involving exenatide have been published. While a new drug application for liraglutide is currently under review by the US FDA, nearly 20 clinical trials focusing on liraglutide had been published by the end of 2008. The most recent of these is the first of the Liraglutide Effect and Action in Diabetes (LEAD) trials to be published. (5)

Question 8

Dr. Brunton: Overall, what did the LEAD trial by Garber et al add to our base of evidence?

Dr. Wender: As a 52-week monotherapy trial, the LEAD trial enabled us to determine the efficacy and safety of liraglutide alone in comparison with a widely used sulfonylurea glimepiride. Thus, we are able to compare the independent effects of these 2 pharmacologic agents over a period of time that is longer than in most clinical trials. This is an important strength of the trial.

Question 9

Dr. Brunton: What was the impact of the treatments on the A1C level?

Dr. Wender: Patients were treated with liraglutide 1.2 or 1.8 mg or glimepiride 8 mg once daily for 52 weeks. From a baseline mean A1C of 8.3-8.4% for all 3 groups, the A1C decreased 0.8% with liraglutide 1.2 mg, 1.1% with liraglutide 1.8 mg, and 0.5% with glimepiride 8 mg (P=0.0014 and P<0.0001vs liraglutide 1.2 and 1.8 mg, respectively; P=0.0046 liraglutide 1.2 vs 1.8 mg). A1C levels generally declined over the first 8-12 weeks. Over weeks 12-52, the A1C level increased slightly and significantly in the liraglutide 1.2 mg and glimepiride 8 mg groups but not the liraglutide 1.8 mg group. Significantly more patients in the liraglutide 1.2 mg (28%) and 1.8 mg (38%) groups achieved an A1C of 6.5% or less at the end of the study compared with glimepiride (16%) (P=0.0025 and P<0.0001 vs liraglutide 1.2 and 1.8 mg, respectively).

As seen with other glucose-lowering agents, the greatest benefit was observed in those not previously treated with medication. Patients previously treated with diet and exercise alone achieved a 1.6% decrease in the A1C with liraglutide 1.8 mg vs a decrease of 0.7% for those previously treated with one oral hypoglycemic agent. The respective reductions in the A1C level were 1.2% vs 0.5% for liraglutide 1.2 mg and 0.9% vs 0.2% for glimepiride.

Question 10

Dr. Brunton: How did the agents affect fasting plasma and postprandial glucose levels?

Dr. Wender: Both the fasting plasma and postprandial glucose levels were significantly reduced in all 3 treatment groups at study end compared to baseline. However, the reductions in the fasting plasma glucose level were significantly more pronounced in the liraglutide 1.2 and 1.8 mg groups compared to the glimepiride group (P=0.027 and P=0.0001, respectively). In fact, significantly more patients in the liraglutide 1.2 and 1.8 mg groups compared with the glimepiride group (38% vs 41% vs 22%, respectively) achieved a fasting plasma glucose level less than 130 mg/dL (P≤0.0001 for each liraglutide group vs glimepiride).

Question 11

Dr. Brunton: Based on these efficacy outcomes, what role in treatment for liraglutide is suggested by this clinical trial?

Dr. Wender: Although results from multiple trials are ideal, these efficacy data suggest that liraglutide may be a more effective treatment option than a sulfonylurea in some patients with T2DM diagnosed within a mean of 5 years as in this trial. Furthermore, for patients previously treated with diet and exercise alone, as well as those treated with only one oral hypoglycemic agent, the treatment benefit with liraglutide appears to be greater than with glimepiride.

Question 12

Dr. Brunton: What other study findings support this possible role for liraglutide?

Dr. Wender: In addition to promoting a 2-3 kg weight loss compared to a 1 kg weight gain with glimepiride, liraglutide was shown to address some of the pathophysiologic mechanisms of T2DM. First, the fasting glucagon level and homeostasis model of insulin resistance, the most commonly used method to estimate insulin resistance, both showed significant decreases with liraglutide but mean increases with glimepiride. Insulin resistance was reduced by 0.65% and 1.35% in the liraglutide 1.2 and 1.8 mg groups, but increased 0.85% in the glimepiride group (P=0.0249 and P=0.0011 vs liraglutide 1.2 and 1.8 mg, respectively). Although we know that decreasing insulin resistance improves the A1C level, we don't know if outcomes are improved. Finally, the homeostasis model of assessment-beta cell and the proinsulin:insulin ratio, both indirect measures of pancreatic beta cell function, showed no significant change between treatments. The reason for this is unclear. Previous studies have demonstrated beneficial effects of liraglutide on pancreatic beta cell function. (6-8)

Question 13

Dr. Brunton: In addition to efficacy, safety is also an important consideration in selecting one therapy over another.

Dr. Wender: Absolutely. Nausea occurred in significantly more patients treated with liraglutide compared with glimepiride (28% vs 9%), and was more commonly reported early during treatment. By week 4, fewer than 10% of patients in the liraglutide 1.8 mg group continued to experience nausea. In the liraglutide 1.2 and 1.8 mg groups, 4% and 2%, respectively, withdrew from the study due to an adverse gastrointestinal event compared with none for glimepiride.

In terms of hypoglycemia, there were no events of major hypoglycemia, ie, hypoglycemia that required third-party assistance, in any of the 3 groups. This has important implications with respect to emergency department visits, hospital admissions, and cost of care. Minor hypoglycemia, which was defined as a plasma glucose < 56 mg/dL, occurred in 12% and 8% of liraglutide 1.2 and 1.8 mg patients, respectively, and 24% of glimepiride patients. This translated into 0.30, 0.25, and 1.96 events per year (P<0.0001 for both liraglutide groups vs glimepiride), respectively.

Finally, because acute pancreatitis can occur in patients with T2DM and 36 cases associated with the GLP-1 exenatide have been reported to the US Food and Drug Administration through August 2008 (9), this was closely monitored in the trial by Garber et al. Two cases of pancreatitis were observed in the liraglutide group. One case occurred after 197 days of liraglutide 1.2 mg and the other after 333 days of liraglutide 1.8 mg. Both patients recovered, and the patient taking liraglutide 1.2 mg continued in the study. It is not clear whether these cases were linked to the drug or diabetes, but this is something we must continue to closely watch over time.

Question 14

Dr. Brunton: Were any other benefits observed with liraglutide relative to glimepiride in the study population?

Dr. Wender: The systolic blood pressure decreased 2.1, 3.6, and 0.7 mm Hg in the liraglutide 1.2 and 1.8 and glimepiride groups (P=0.2912 and P<0.0118 vs glimepiride), respectively. The mechanism for this was not investigated in the trial and remains unclear. However, both body weight and systolic blood pressure declined quickly after initiating liraglutide. Since blood pressure is often difficult to control in patients with T2DM, any treatment that contributes to a reduction is beneficial. Diastolic blood pressure, on the other hand, decreased slightly but not

significantly in any of the 3 groups. The pulse rate increased by 3.2, 1.6, and 0.4 beats per minute (*P*=0.0027 and *P*=0.14 vs glimepiride), respectively.

Question 15

Dr. Brunton: In light of these data, if a physician determines that liraglutide is a better option than a sulfonylurea for a particular patient, when and how would liraglutide be initiated?

Dr. Wender: As an alternative to a sulfonylurea, liraglutide could be used as second-line therapy for a patient who does not achieve glycemic control with the combination of lifestyle intervention and maximally tolerated doses of metformin. Liraglutide could also be used as an option for a patient with a contraindication to metformin. Thus, liraglutide would be used in combination with lifestyle intervention as initial therapy for a patient with an A1C < 8.5%. For an A1C above 8.5%, insulin is generally preferred.

As in this study, liraglutide would be initiated at a dose of 0.6 mg once daily for 1 week and increased by 0.6 mg every week to a dose of 1.2 or 1.8 mg once daily. The titration of liraglutide can be adjusted based on patient tolerability.

Question 16

Dr. Brunton: Where do you anticipate using liraglutide in the treatment of your patients with T2DM?

Dr. Wender: I expect to use liraglutide or exenatide as recommended by the ADA/EASD panel as one of the preferred therapies to be added to lifestyle and metformin as part of a treat-to-success approach for patients with T2DM.

In addition, I expect to use liraglutide or exenatide as an alternative to a sulfonylurea as we previously discussed. I also think liraglutide might be an option for a patient who is intolerant of metformin and for whom I'd like to avoid insulin, such as when weight is a special concern. Although the results of head-to-head studies of exenatide and liraglutide have not yet been published, liraglutide provides the added benefits of once-daily administration and possibly a lower incidence of adverse gastrointestinal effects.

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