DIABETES CARE

LEAD-2: liraglutide compared with glimepiride, when added to metformin

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 Liraglutide is a once-daily glucagon-like peptide-1 receptor agonist that is as-yet unlicensed in the UK.

2 The investigators of this study compared the effects of liraglutide (either 0.6, 1.2 or 1.8 mg once-daily), glimepiride (4 mg once-daily) and placebo in people with type 2 diabetes, when each was given in combination with metformin.

3 Overall, 1091 participants with an HbA_{1c} level of 7–11% (with previous oral monotherapy) or 7–10% (with oral combination therapy) were randomly assigned to treatment groups.

4 Compared with placebo, all doses of liraglutide were associated with significant reductions in HbA_{1c} levels ($P<0.0001$). The mean reduction in HbA_{1c} for those receiving liraglutide 1.8 mg or 1.2 mg, and those receiving glimepiride was 1.0%. Liraglutide 1.2 and 1.8 mg treatments met criteria for non-inferiority to glimepiride.

5 Body weight increased in the glimepiride group (+1.0 kg), whereas it decreased in all liraglutide groups (–1.8 to –2.8 kg; $P<0.0001$).

6 The incidence of minor hypoglycaemia experienced with liraglutide (approximately 3%) was comparable to that in the placebo group, and was lower than that experienced by the glimepiride group (17%; $P<0.0001$).

7 Nausea was reported by a greater proportion of the liraglutide groups than the placebo group. The incidence did, however, decline over time.

Nauck M, Frid A, Hermansen K et al (2009) Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care* **32**: 84–90

Liraglutide: LEADing the way?

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Results from the LEAD (Liraglutide Effect and Action in Diabetes) programme of studies, which explores where the long-acting glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide may fit into the current therapeutic armamentarium for type 2 diabetes, are beginning to reach the literature and deserve consideration. Liraglutide is currently unlicensed in the UK, but the Committee for Medicinal Products for Human Use recently recommended marketing authorisation.

When considering the background therapy used in each trial, the order in which the six trials are numbered is not terribly intuitive (*Table 1*), but the programme in its entirety does provide relevant clinical context for many patients with type 2 diabetes in the clinic.

In the two studies summarised in this edition of *Diabetes Digest*, liraglutide was shown to hold promise. In LEAD-2, liraglutide at a dose of 0.6, 1.2 or 1.8 mg was compared with glimepiride 4 mg when either was added to metformin 1 g twice-daily in people with less than optimally controlled diabetes (HbA_{1c} ≥7%). Weight loss was achieved in all the liraglutide-treated groups while those treated with glimepiride gained weight. Rates of hypoglycaemia were also significantly lower in liraglutide-treated participants (3% vs. 17%; $P<0.0001$). At the end of the study, 35% of participants treated with liraglutide 1.2 mg and 42% treated with 1.8 mg reached the American Diabetes Association HbA_{1c} target of <7%, compared with 36% of patients receiving glimepiride 4 mg.

In the LEAD-3 study, monotherapy with liraglutide proved more effective at improving HbA_{1c} levels and was associated with lower hypoglycaemia rates, lower blood pressure and lower body weight than glimepiride.

As GLP-1 receptor agonists stimulate glucose-dependent insulin secretion, hypoglycaemia is an uncommon side-effect when the agents are used as monotherapy or in combination with metformin. Nausea is the limiting problem, although from these data it appears that with liraglutide this can often be overcome by starting and maintaining a lower dose until tolerance develops.

A key consideration will be how durable and sustainable the early benefits of improved glycaemic control, reduced hypoglycaemia and weight loss are, and also, very importantly, whether there are major outcome benefits in terms of large- or small-vessel event rates. Nonetheless, these early trial findings look promising and we should keep alert for further data.

Table 1. Summary of the LEAD (Liraglutide Effect and Action in Diabetes) study programme.

Study name	Background therapy	Add-on therapy	Comparator
LEAD-1	Glimepiride	Liraglutide	Rosiglitazone or placebo
LEAD-2	Metformin	Liraglutide	Glimepiride or placebo
LEAD-3	None	Liraglutide	Glimepiride
LEAD-4	Metformin and rosiglitazone	Liraglutide	Placebo
LEAD-5	Metformin and glimepiride	Liraglutide	Insulin glargine or placebo
LEAD-6	Metformin, glimepiride or both	Liraglutide	Exenatide

"Participants receiving liraglutide experienced a reduction in body weight, whereas those in the glimepiride group gained weight."

THE LANCET

LEAD-3: liraglutide compared with glimepiride monotherapy

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 The current authors investigated the safety and efficacy of two doses of the glucagon-like peptide-1 receptor agonist liraglutide (1.2 and 1.6 mg once-daily) by comparing its effects with those of glimepiride in a 52-week, double-blind, parallel-group, randomised, controlled trial.

2 Overall, 746 people with type 2 diabetes were randomised to different treatment arms: liraglutide 1.2 mg (n=251); liraglutide 1.8 mg (n=247); glimepiride 8 mg (n=248).

3 Patients were eligible for inclusion if they had suboptimal glycaemic control with either diet and exercise approaches (36.5% of those randomised) or monotherapy with up to half of the maximal dose (63.5%).

4 Both doses of liraglutide were associated with significantly greater reductions in HbA_{1c} than glimepiride (1.2 mg: between-group difference –0.33%; P=0.0014; 1.8 mg: between-group difference –0.62%; P<0.0001).

5 Participants receiving liraglutide experienced a reduction in body weight, whereas those in the glimepiride group gained weight. For each liraglutide group, the change in body weight was significantly different to that in the glimepiride group.

6 Nausea was experienced by significantly more participants in the liraglutide groups than in the glimepiride group (P<0.0001).

7 The authors concluded that liraglutide is safe and efficacious as an initial therapy for people with type 2 diabetes.

Garber A, Henry R, Ratner R et al (2009) Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* **373**: 473–81

DIABETOLOGIA

Normalisation of glycaemia improves responsiveness to GIP and GLP-1

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The responsiveness of the beta-cell to glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) is known to be diminished in people with type 2 diabetes.

2 The current investigators aimed to determine whether near-normalisation of blood glucose levels with insulin over 4 weeks would ameliorate this (mean blood glucose level achieved: 7.4 mmol/L).

3 GLP-1 and GIP responsiveness were investigated using hyperglycaemic clamps before and after insulin treatment.

4 Improvement in beta-cell responsiveness by a factor of 3–4 was observed for both GLP-1 and GIP.

Hojberg PV, Vilsboll T, Rabol R et al (2009) Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. *Diabetologia* **52**: 199–207

JACC

Fenofibrate not linked with improved carotid IMT

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓

1 The current study was designed to assess the effect of long-term treatment with fenofibrate on surrogate markers of atherosclerosis, inflammation and endothelial function in people with type 2 diabetes.

2 Overall, 170 participants from the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study were randomised to receive either fenofibrate 200 mg/day or placebo.

3 Carotid intima-media thickness (IMT) and a range of biochemical markers were measured at baseline and at years 2 and 5.

4 The authors found that fenofibrate was not associated with beneficial changes in carotid IMT, large artery stiffness or markers of inflammation and endothelial function, relative to placebo.

Hiukka A, Westerbacka J, Leinonen ES et al (2008) Long-term effects of fenofibrate on carotid intima-media thickness and augmentation index in subjects with type 2 diabetes mellitus. *J Am Coll Cardiol* **52**: 2190–7

DIABETES CARE

Prediction tool for mortality risk

	✓✓✓
	✓✓✓
	✓✓✓

1 The authors aimed to generate a tool that could be used to predict mortality risk when making treatment decisions in people with type 2 diabetes.

2 More than 33 000 people with type 2 diabetes who were prescribed oral blood glucose lowering monotherapy between 1998 and 2006 were identified on an electronic health record (EHR). Data on mortality were sourced from the EHR and a social security database.

3 The prediction tool, based on medication class and a series of other mortality predictors, was created using a Cox proportional hazards regression model.

4 The tool was tested on the cohort and found to have a concordance statistic of 0.752 (where 0.5 represents chance and 1.0 perfect prediction).

Wells BJ, Jain A, Arrigain S et al (2008) Predicting 6-year mortality risk in patients with type 2 diabetes. *Diabetes Care* **31**: 2301–6

METABOLISM

Exploring bone stiffness in men with type 2 diabetes

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 It is known that people with type 2 diabetes have a greater risk of bone fracture than their counterparts without diabetes.

2 The current authors explored the relationship between bone stiffness and variables, including serum bioavailable testosterone concentration, age, duration of diabetes and HbA_{1c} level, in 294 men with type 2 diabetes.

3 Multiple regression analysis established smoking status and serum bioavailable testosterone concentration as independent determinants of bone stiffness.

4 Current smoking was associated with a lower stiffness index than previous smoking or non-smoking. Higher serum bioavailable testosterone levels were associated with a higher bone stiffness index.

Asano M, Fukui M, Hosoda H et al (2008) Bone stiffness in men with type 2 diabetes mellitus. *Metabolism* **57**: 1691–5

AGING CLINICAL AND EXPERIMENTAL RESEARCH

Type 2 diabetes linked with higher bone mineral density

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The authors of the present study examined fracture rates and bone mineral density (BMD) in older, post-menopausal, obese woman with type 2 diabetes.

2 Overall, 111 women with type 2 diabetes, and 91 control participants without diabetes, were recruited from centres in Spain. Data on BMD and vertebral, hip and non-vertebral fractures were collected using X-ray, medical notes and quantitative ultrasound.

3 Type 2 diabetes was associated with an increased lumbar BMD (P=0.035), but not with differences in proximal femur BMD.

4 Type 2 diabetes was not associated with an increased rate of vertebral, hip or non-vertebral fractures.

Sosa M, Saavedra P, Jodar E et al (2009) Bone mineral density and risk of fractures in aging, obese post-menopausal women with type 2 diabetes. The GIUMO Study. *Aging Clin Exp Res* **21**: 27–32

DIABETES RESEARCH AND CLINICAL PRACTICE

Lipoprotein profile predicts type 2 diabetes

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The current authors assessed the value of lipid profiles determined by nuclear magnetic resonance (NMR) in predicting type 2 diabetes.

2 Over 800 participants in the Melbourne Collaborative Cohort Study were eligible for inclusion. Fifty-nine developed type 2 diabetes during the study; the remainder acted as a control group.

3 The investigators identified an atherogenic lipoprotein profile from NMR data that predicted the incidence of type 2 diabetes in the cohort.

4 However, the profile identified did not improve diabetes prediction beyond that from considering conventionally measured triglyceride levels.

Hodge AM et al (2009) NMR-determined lipoprotein subclass profile predicts type 2 diabetes. *Diabetes Res Clin Pract* **83**: 132–9

DIABETES CARE

Investigating the relationship between depression and type 2 diabetes

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The current authors undertook a systematic review to investigate the proposed bidirectional relationship between depression and type 2 diabetes.

2 A literature search was conducted for publications between 1950 and 2007 that investigated the relationships between the conditions using a comparative, prospective study design.

3 Risk estimates were pooled in two sets: type 2 diabetes predicting depression, and depression predicting type 2 diabetes.

4 Overall, 42 publications were reviewed by the investigators. Of these, seven met the eligibility criteria for exploring diabetes as a predictor of depression. Thirteen met the criteria for inclusion in the consideration of depression as a predictor of type 2 diabetes. The included publications represented 6414 and 6916 cases, respectively.

5 The relative risk of incident type 2 diabetes associated with baseline depression was found to be 1.60 (95% confidence interval [CI] 1.37–1.88). The relative risk of incident depression associated with baseline type 2 diabetes was 1.15 (95% CI 1.02–1.30).

6 The authors concluded that depression is associated with a marked increase in the risk of type 2 diabetes. In contrast, baseline type 2 diabetes is associated with only a small increase in the risk of depression.

Mezuk B, Eaton WW, Albrecht S et al (2008) Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care* **31**: 2383–90

"Depression is associated with a marked increase in the risk of type 2 diabetes. In contrast, baseline type 2 diabetes is associated with only a small increase in the risk of depression."