Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial

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Summary

Background Dulaglutide and liraglutide, both glucagon-like peptide-1 (GLP-1) receptor agonists, improve glycaemic control and reduce weight in patients with type 2 diabetes. In a head-to-head trial, we compared the safety and efficacy of once-weekly dulaglutide with that of once-daily liraglutide in metformin-treated patients with uncontrolled type 2 diabetes.

Methods We did a phase 3, randomised, open-label, parallel-group study at 62 sites in nine countries between June 20, 2012, and Nov 25, 2013. Patients with inadequately controlled type 2 diabetes receiving metformin (≥1500 mg/day), aged 18 years or older, with glycated haemoglobin (HbA_{1c}) 7·0% or greater (≥53 mmol/mol) and 10·0% or lower (≤86 mmol/mol), and body-mass index 45 kg/m² or lower were randomly assigned to receive once-weekly dulaglutide (1·5 mg) or once-daily liraglutide (1·8 mg). Randomisation was done according to a computer-generated random sequence with an interactive voice response system. Participants and investigators were not masked to treatment allocation. The primary outcome was non-inferiority (margin 0·4%) of dulaglutide compared with liraglutide for change in HbA_{1c} (least-squares mean change from baseline) at 26 weeks. Safety data were collected for a further 4 weeks' follow-up. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT01624259.

Findings We randomly assigned 599 patients to receive once-weekly dulaglutide (299 patients) or once-daily liraglutide (300 patients). 269 participants in each group completed treatment at week 26. Least-squares mean reduction in HbA_{1c} was –1·42% (SE 0·05) in the dulaglutide group and –1·36% (0·05) in the liraglutide group. Mean treatment difference in HbA_{1c} was –0·06% (95% CI –0·19 to 0·07, $p_{non\text{-}inferiority}$<0·0001) between the two groups. The most common gastrointestinal adverse events were nausea (61 [20%] in dulaglutide group *vs* 54 [18%] in liraglutide group), diarrhoea (36 [12%] *vs* 36 [12%]), dyspepsia (24 [8%] *vs* 18 [6%]), and vomiting (21 [7%] *vs* 25 [8%]), with similar rates of study or study drug discontinuation because of adverse events between the two groups (18 [6%] in each group). The hypoglycaemia rate was 0·34 (SE 1·44) and 0·52 (3·01) events per patient per year, respectively, and no severe hypoglycaemia was reported.

Interpretation Once-weekly dulaglutide is non-inferior to once-daily liraglutide for least-squares mean reduction in HbA_{1c}, with a similar safety and tolerability profile.

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Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists have been commercially available since 2005, with exenatide twice daily being the first drug in this class.[1] GLP-1 receptor agonists stimulate glucose-dependent insulin secretion, reduce glucagon secretion, and slow gastric emptying, resulting in improved glycaemic control and modest weight reduction with a low risk of hypoglycaemia.[2] Available GLP-1 receptor agonists differ in duration of action, administration frequency, timing and ease of dosing, effectiveness, tolerability, and immunogenicity. Short-acting GLP-1 receptor agonists have been reported to significantly reduce postprandial glucose concentrations, which is presumed to be secondary to effects on inhibition of gastric emptying.[3–5] Up to now, longer-acting GLP-1 receptor agonists with increased continuity of action have shown a more pronounced effect on fasting glucose than have shorter-acting drugs, mediated through insulinotropic and glucagonostatic actions.[3–6] This class of drugs is typically initiated when patients no longer achieve and maintain glycaemic control with one or more oral antihyperglycaemic drugs,[7] and is often the first injectable drug for a patient. Additionally, the GLP-1 receptor agonist class is increasingly being used in combination with insulin.[8–10] The frequency of administration ranges from twice daily to once weekly.[1,11,12] Study findings have shown superiority of the once-weekly GLP-1 receptor agonists exenatide and dulaglutide (Eli Lilly, Indianapolis, IN, USA), to twice-daily exenatide.[3,6,13] However, in head-to-head non-inferiority trials, the two approved once-weekly GLP-1 receptor agonists (exenatide and albiglutide;

GlaxoSmithKline, Wilmington, DE, USA) have not shown non-inferiority to once-daily liraglutide.[12,14]

Dulaglutide is a once-weekly GLP-1 receptor agonist in development for type 2 diabetes.[15–17] By contrast with native GLP-1, dulaglutide is resistant to dipeptidyl peptidase-4 degradation and has a large size that slows absorption and minimises renal clearance, resulting in a soluble formulation with a prolonged half-life of about 5 days, making it suitable for once-weekly subcutaneous administration.[15] Findings from long-term phase 3 trials showed that once-weekly dulaglutide 1·5 mg had better reduction of glycated haemoglobin (HbA_{1c}) than did metformin, sitagliptin, and exenatide twice daily, with small weight loss and a safety and tolerability profile that is consistent with the GLP-1 receptor agonist class.[13,18,19] Dulaglutide has also been shown to have significant, sustained effects on both fasting and postprandial glucose concentrations.[13,18,19]

In the Assessment of Weekly AdministRation of LY2189265 (dulaglutide) in Diabetes-6 (AWARD-6) study, we aimed to assess the non-inferiority of once-weekly dulaglutide compared with once-daily liraglutide in patients with type 2 diabetes receiving concomitant metformin therapy.

Methods

Study design and participants

AWARD-6 was a randomised, open-label, parallel-group, multicentre, phase 3, non-inferiority study, comparing the safety and efficacy of once-weekly dulaglutide with once-daily liraglutide in metformin-treated patients with uncontrolled type 2 diabetes. The study had three periods: screening (2 weeks), randomisation (at week 0) immediately followed by treatment (26 weeks), and safety follow-up (4 weeks). Data were collected from study participants between June 20, 2012, and Nov 25, 2013. Patients were recruited from 62 sites in nine countries (Czech Republic, Germany, Hungary, Mexico, Poland, Romania, Spain, Slovakia, and the USA).

Eligible patients at screening had type 2 diabetes (HbA_{1c} ≥7·0% [≥53 mmol/mol] and ≤10·0% [≤86 mmol/mol]), were 18 years or older, had a body-mass index (BMI) of 45 kg/m² or less, and were receiving a stable dose of metformin (≥1500 mg/day) for 3 months or longer. Key exclusion criteria included use of other antihyperglycaemic drugs, serum calcitonin concentration of 5·79 pmol/L or higher, serum creatinine concentration of 132·6 μmol/L or higher (men) or 123·8 μmol/L or higher (women), creatinine clearance of less than 60 mL/min, or history of pancreatitis or recent cardiovascular event (full inclusion and exclusion criteria listed in appendix).

See Online for appendix

The protocol was approved by local institutional review boards; all patients provided written informed consent. The study was done in accordance with the Declaration of Helsinki guideline on good clinical practices and country-specific requirements.[20]

Randomisation and masking

We randomly assigned participants in a 1:1 ratio to receive subcutaneous injections of once-weekly dulaglutide 1·5 mg or once-daily liraglutide 1·8 mg according to a computer-generated random sequence with use of an interactive voice response system. Randomisation was stratified by country and baseline HbA_{1c} (≤8·5% [≤69 mmol/mol] and >8·5% [>69 mmol/mol]). An open-label design was used and participants, treating physicians, investigators, and site staff were not masked to treatment allocation. The study statistician and medical personnel from the sponsor were masked to the treatment allocation until after database lock and analyses were completed.

Procedures

Patients were given a prefilled syringe (dulaglutide) or pen (liraglutide) to be self-administered. Dulaglutide was started at the full 1·5 mg once-weekly dose. Liraglutide was uptitrated from 0·6 mg/day in week 1, to 1·2 mg/day in week 2, and then to 1·8 mg/day in week 3. Patients unable to tolerate the full dose of study drug were required to discontinue the study drug but encouraged to remain in the study to collect safety data for the full intention-to-treat population. Patients continued metformin therapy (≥1500 mg/day and up to the highest dose allowed per local label) throughout the study. We assessed compliance to treatment regimen by review of patients' diaries and returned, unused study drugs; we defined treatment compliance as taking at least 75% of the study drug per visit.

Patients with severe, persistent hyperglycaemia during the study could initiate additional glycaemic rescue therapy according to prespecified criteria (appendix). The antihyperglycaemic intervention was determined by the investigator; use of other non-study GLP-1 receptor agonists or inhibitors of dipeptidyl peptidase-4 was not permitted.

An independent external committee adjudicated deaths and non-fatal cardiovascular adverse events in a masked manner, with prespecified event criteria based on the preponderance of the evidence and clinical knowledge and experience. An independent external committee adjudicated adverse events of severe or serious abdominal pain, suspected or definite acute or chronic pancreatitis, and lipase or amylase concentrations of three times the upper limit of normal or higher. Serum calcitonin was measured throughout the study.

Patients given dulaglutide were tested for the development of dulaglutide antidrug antibodies. Positive samples were assessed for dulaglutide-neutralising activity and cross-reactivity with native GLP-1.

Outcomes

The primary efficacy measure was change in HbA_{1c} from baseline to week 26 between once-weekly dulaglutide and once-daily liraglutide. Secondary efficacy measures were the proportion of patients

achieving HbA_{1c} targets of less than 7·0% (<53 mmol/mol) or 6·5% or less (≤48 mmol/mol); change in fasting plasma serum glucose (evaluated at a central laboratory), seven-point self-monitored plasma glucose profiles, bodyweight, BMI, and β-cell function assessed with the homoeostasis model assessment (HOMA2-%B). Safety assessments included adverse events, dulaglutide antidrug antibodies, lipids, vital signs (heart rate and blood pressure), electrocardiogram (ECG), and occurrence of severe, persistent hyperglycaemia requiring rescue drugs. Adverse events of special interest were pancreatitis, C-cell hyperplasia and C-cell neoplasms, cardiovascular events, allergic or hypersensitivity reactions, and hypoglycaemia. Total hypoglycaemia was defined as plasma glucose concentration of 3·9 mmol/L or less, or signs or symptoms attributable to hypoglycaemia.[21] Severe hypoglycaemia was an event needing assistance of another person to actively give therapy as determined by the investigator.[21]

We assessed health-related quality of life with exploratory patient-reported outcome measures (European quality of life 5 dimensions, ability to perform physical activities of daily living, and impact of weight on self-perception).[22–24] The proportion of patients who achieved HbA_{1c} of less than 7·0% without persistent nausea or vomiting (defined as patients who developed nausea or vomiting after randomisation that had not resolved by week 4 of treatment and was longer than 10 days in duration, or that led to study drug or study discontinuation) was also assessed as an exploratory measure.

Statistical analyses

The primary objective was non-inferiority of dulaglutide to liraglutide for HbA_{1c} change from baseline. To show non-inferiority with 90% power, we calculated that 222 completers per treatment group (444 in total) were required at 26 weeks, assuming no difference in HbA_{1c} between dulaglutide and liraglutide, 0·4% margin of non-inferiority, common SD of 1·3% for change in baseline HbA_{1c}, and 0·05 two-sided significance level. Assuming 25% dropout, we estimated that 296 randomly assigned patients per treatment group would be needed. After non-inferiority, serial gatekeeping was used to assess superiority of dulaglutide; type I error rate was controlled at 0·025 (one-sided).[25,26]

Efficacy and safety analyses were done with the intention-to-treat population (all randomly assigned patients who took one or more doses of study drug). For efficacy and hypoglycaemia measures, we used only data obtained before rescue drugs were given. The primary efficacy analysis used a mixed model for repeated measures (MMRM) with treatment, country, visit, and treatment-by-visit interaction as fixed effects; baseline as covariate; and patient as random effect. The secondary sensitivity analysis for the primary endpoint was ANCOVA with country and treatment as fixed effects and baseline as a covariate with the last (postbaseline HbA_{1c})

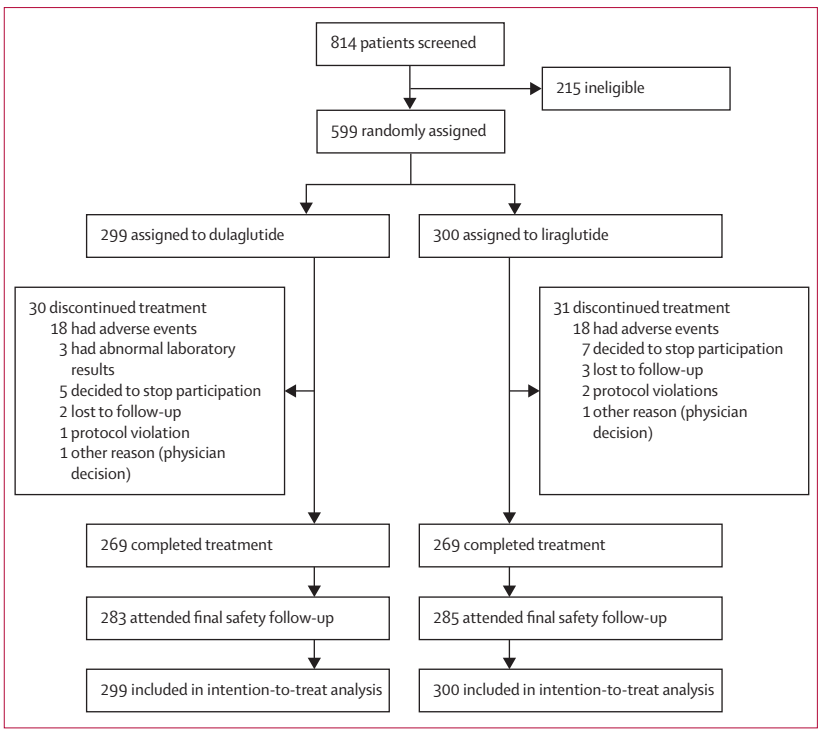

Figure 1: **Trial profile**

	Dulaglutide (n=299)	Liraglutide (n=300)
Sex		
Men	138 (46%)	149 (50%)
Women	161 (54%)	151 (50%)
Age (years)	56·5 (9·3)	56·8 (9·9)
≥65 years	51 (17%)	60 (20%)
Race		
American Indian or Alaskan Native	20 (7%)	23 (8%)
Asian	1 (<1%)	0
Black or African American	21 (7%)	16 (5%)
Multiple	1 (<1%)	2 (1%)
White	256 (86%)	259 (86%)
Ethnic origin*		
Hispanic or Latino	75 (25%)	72 (24%)
Not Hispanic or Latino	221 (75%)	223 (76%)
Weight (kg)	93·8 (18·2)	94·4 (19·0)
BMI (kg/m²)	33·5 (5·1)	33·6 (5·2)
Diabetes duration (years)	7·1 (5·4)	7·3 (5·4)
HbA_{1c} (%)	8·1% (0·8)	8·1% (0·8)
HbA_{1c} (mmol/mol)	65 (8·8)	65 (8·8)
Fasting serum glucose concentration (mmol/L)	9·3 (2·2)	9·2 (2·3)
Systolic blood pressure (mm Hg)	132·2 (15·0)	130·9 (15·1)
Diastolic blood pressure (mm Hg)	79·9 (9·5)	79·1 (9·2)
Metformin dose (mg)	2021 (418)	2068 (452)

Data are n (%) or mean (SD). BMI=body-mass index. HbA_{1c}=glycated haemoglobin. *Data for ethnic origin were not collected for four patients in the dulaglutide group and five patients in the liraglutide group.

Table 1: **Baseline characteristics**

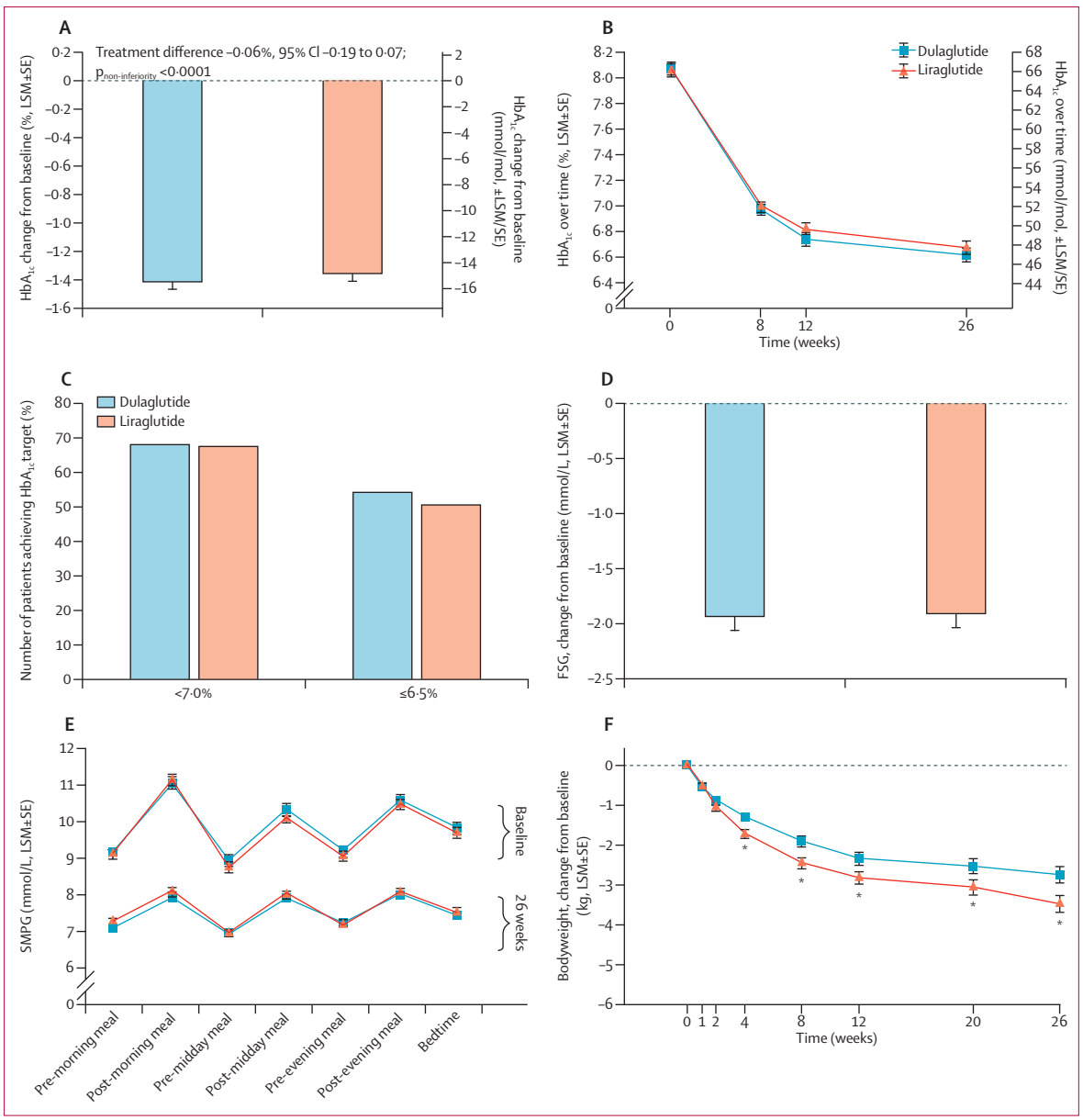

Figure 2: **Trial outcome measures**
(A) Change in HbA_{1c} from baseline to week 26 (MMRM). (B) HbA_{1c} values from baseline to week 26 (MMRM). (C) Percentage of patients achieving HbA_{1c} targets. (D) Change in fasting plasma glucose concentrations from baseline to week 26, as measured by a central laboratory. (E) Seven-point self-measured plasma glucose by time of day. (F) Bodyweight from baseline to 26 weeks (MMRM). HbA_{1c}=glycated haemoglobin. MMRM=mixed model for repeated measures. LSM=least-squares mean. FSG=fasting serum glucose. SMPG=seven-point self-measured glucose. *p<0·05.

observation carried forward (LOCF). MMRM and ANCOVA were used for change in bodyweight. Analyses for other measures used MMRM.

We analysed the percentage of patients achieving HbA_{1c} targets (LOCF) with a repeated logistic regression model with treatment, country, visit, treatment-by-visit interaction, and baseline HbA_{1c} as a covariate. Total hypoglycaemia included events that were documented symptomatic, documented asymptomatic, probable, or severe.[21] We analysed hypoglycaemia rates with a generalised linear model with negative binomial distribution. The percentage of patients with adverse events was analysed with use of a χ^2 test, unless insufficient data were available to meet analysis assumptions, then Fisher's exact test was used. The two-sided significance level was 0·05 for secondary endpoints. Least-squares means (LSM) for HbA_{1c}, fasting serum glucose, and bodyweight were calculated.

This study is registered with ClinicalTrials.gov, number NCT01624259.

	Dulaglutide (n=299)			Liraglutide (n=300)			Dulaglutide *vs* liraglutide	
	Baseline	Change from baseline to week 26	p value	Baseline	Change from baseline to week 26	p value	Mean difference	p value
HbA_{1c} (%)	8·1% (0·8)	−1·42% (0·05)	<0·0001	8·1% (0·8)	−1·36% (0·05)	<0·0001	−0·06% (−0·19 to 0·07)	<0·0001*
HbA_{1c} (mmol/mol)	65 (8·8)	−16 (0·55)	<0·0001	65 (8·8)	−15 (0·55)	<0·0001	−0·66 (−2·08 to 0·77)	<0·0001*
Fasting serum glucose concentration (mmol/L)	9·3 (2·2)	−1·93 (0·12)	<0·0001	9·2 (2·3)	−1·90 (0·12)	<0·0001	−0·03 (−0·32 to 0·25)	0·83
Postprandial plasma glucose concentration (mmol/L)	10·7 (0·1)	−2·56 (0·09)	<0·0001	10·6 (0·1)	−2·43 (0·09)	<0·0001	−0·13 (−0·36 to 0·10)	0·26
Bodyweight (kg)	93·8 (18·2)	−2·90 (0·22)	<0·0001	94·4 (19·0)	−3·61 (0·22)	<0·0001	0·71 (0·17 to 1·26)	0·011

Data are least-squares mean (SE) or mean difference (95% CI). HbA_{1c}=glycated haemoglobin. *p value is for non-inferiority of dulaglutide versus liraglutide.

Table 2: **Comparison of trial outcome measures between dulaglutide and liraglutide**

Role of the funding source

The study sponsor was involved in study design, data collection, data review, data analysis, and drafting of the report. All authors had full access to the data and approved the report for publication. KMD and JLF had final responsibility for the decision to submit for publication.

Results

In AWARD-6, 599 eligible patients were randomly assigned to receive dulaglutide 1·5 mg (299 patients) or liraglutide 1·8 mg (300 patients; figure 1). 30 (10%) patients taking dulaglutide and 31 (10%) taking liraglutide discontinued the study or study drug before 26 weeks; adverse events were the most common reason in both groups (dulaglutide, 18 [6%]; liraglutide, 18 [6%]).

During the treatment period, 19 patients (six receiving dulaglutide [2%] and 13 [4%] receiving liraglutide) received an alternative antihyperglycaemic drug for any reason. One patient in the dulaglutide group and three in the liraglutide group needed glycaemic rescue therapy. Efficacy and hypoglycaemia data were censored after initiation of an alternative antihyperglycaemic drug. Patients who discontinued the study before the end of the treatment period had an early termination visit and then returned 4 weeks later for a final safety follow-up visit. Table 1 shows baseline characteristics of the two groups. Overall, 98·2% of patients in the dulaglutide group and 97·5% in the liraglutide group were considered compliant with study drug.

Both dulaglutide and liraglutide significantly reduced HbA_{1c} from baseline (figure 2, table 2). The HbA_{1c} reduction with dulaglutide was non-inferior, but not superior, to that achieved by liraglutide, with a between-group difference in HbA_{1c} reduction from baseline of −0·06% (95% CI −0·19 to 0·07, $p_{non\text{-}inferiority}$<0·0001), equivalent to −0·66 mmol/mol. Decreases in HbA_{1c} over time were similar between groups (figure 2).

We noted similar results with the ANCOVA (LOCF) sensitivity analysis. At 26 weeks, 200 of 293 (68%) patients in the dulaglutide group achieved HbA_{1c} targets of less than 7·0% (<53 mmol/mol) compared with 199 of 293 (68%) in the liraglutide group; 160 (55%) patients achieved HbA_{1c} targets of 6·5% or less (≤48 mmol/mol) in the dulaglutide group compared with 149 (51%) in the liraglutide group (figure 2). Both dulaglutide and liraglutide significantly reduced fasting serum glucose concentrations between baseline and 26 weeks, with no significant difference between groups (figure 2, table 2). Seven-point self-monitored plasma glucose profiles measured at baseline and 26 weeks did not differ significantly between treatments at any time point measured (figure 2, table 2). At 26 weeks, the LSM change in postprandial plasma glucose concentration did not differ significantly between groups (table 2). The LSM change from baseline in bodyweight (ANCOVA [LOCF]) was −2·90 kg (SE 0·22) for dulaglutide and −3·61 kg (0·22) for liraglutide (figure 2, table 2); between-group differences for change from baseline in BMI were consistent with weight findings (data not shown). Similar improvements in HOMA2%B were observed with dulaglutide and liraglutide (appendix).

Five (2%) patients in the dulaglutide group and 11 (4%) in the liraglutide group had serious adverse events (table 3, appendix). No patients died between randomisation and final follow-up. The most frequent treatment emergent adverse events were generally gastrointestinal, with nausea, diarrhoea, vomiting, and dyspepsia being the most common (table 3); there were no differences between groups. The frequency of nausea peaked at week 1 in both groups and decreased thereafter (figure 3). In both groups, most gastrointestinal events were mild to moderate in severity and transient in nature. Nine (3%) patients in the dulaglutide group and 13 (4%) in the liraglutide group discontinued the study or study drug because of a gastrointestinal adverse event, with nausea being the most common reason (five patients in each group). The proportion of patients who achieved HbA_{1c} less than 7·0% without persistent nausea or vomiting did not differ between groups (185 of 296 [63%] patients receiving dulaglutide *vs* 185 of 295 [63%] receiving liraglutide).

Total hypoglycaemia (defined as a plasma glucose concentration ≤3·9 mmol/L with or without symptoms)

	Dulaglutide (n=299)	Liraglutide (n=300)	p value
Deaths	0	0	
Serious AEs*	5 (2%)	11 (4%)	0·13
Patients with at least one treatment-emergent AE	185 (62%)	189 (63%)	0·78
Treatment-emergent AEs (≥5% patients in either group)			
Gastrointestinal disorders	107 (36%)	107 (36%)	0·98
Nausea	61 (20%)	54 (18%)	0·46
Diarrhoea	36 (12%)	36 (12%)	0·99
Vomiting	21 (7%)	25 (8%)	0·55
Dyspepsia	24 (8%)	18 (6%)	0·33
Constipation	11 (4%)	17 (6%)	0·25
Nasopharyngitis	23 (8%)	21 (7%)	0·75
Headache	22 (7%)	25 (8%)	0·66
Back pain	11 (4%)	15 (5%)	0·43
Decreased appetite	16 (5%)	20 (7%)	0·50
Patients who discontinued study or study drug because of AEs	18 (6%)	18 (6%)	0·99
Vital signs (mean change from baseline; SE)†			
Systolic blood pressure (mm Hg)	−3·36 (0·7)	−2·82 (0·7)	0·60
Diastolic blood pressure (mm Hg)	−0·22 (0·4)	−0·31 (0·4)	0·88
Heart rate (bpm)	2·37 (0·4)	3·12 (0·4)	0·25
ECG PR interval (ms; mean change from baseline; SE)†	3·8 (0·81)	3·3 (0·80)	0·62
Pancreatic enzymes (median change; IQR)‡			
Total amylase (U/L)	7 (0–14)	6 (0–13)	0·19
Lipase (U/L)	7 (1–18)	11 (2–23)	0·012
Patients with treatment-emergent abnormal changes in pancreatic enzymes			
Total amylase	18 (6%)	20 (7%)	0·75
Lipase§	63 (25%)	84 (33%)	0·052
Patients with pancreatic enzyme concentration of ≥3×ULN			
Total amylase	1 (<1%)	0	0·50
Lipase	11 (4%)	9 (3%)	0·64
Treatment-emergent dulaglutide antidrug antibodies¶			
Dulaglutide antidrug antibodies	3 (1%)	..	
Dulaglutide neutralising antidrug antibodies	2 (1%)	..	
nsGLP-1 neutralising antibodies	0	..	

Data are n (%) unless otherwise specified. AEs=adverse events. ULN=upper limit of normal. NA=not applicable. nsGLP1=native sequence glucagon-like peptide-1. *Reported serious AEs are listed in the appendix. †Data are least-squares mean change (SE). ‡Data are last observation carried forward, median change (IQR). §252 patients in the dulaglutide group and 256 in the liraglutide group had a lipase measurement. ¶These values include all postbaseline observations including the safety follow-up.

Table 3: **Safety assessments and vital signs up to 26 weeks' follow-up**

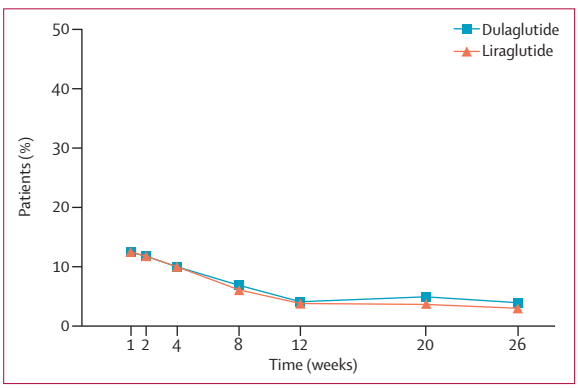

Figure 3: **Frequency of nausea from baseline to week 26**
Only patients active in the study and taking study drug are counted within each interval.

occurred in 26 (9%) patients given dulaglutide and 17 (6%) patients given liraglutide, with a mean event rate of 0·34 (SE 1·44) events per patient per year for dulaglutide compared with 0·52 (3·01) for liraglutide (appendix); no patients had severe hypoglycaemia in the study period.

No cases of adjudicated pancreatitis or pancreatic cancer were reported. Treatment with dulaglutide or liraglutide increased total amylase concentration from baseline (table 3). Lipase concentration was significantly higher at endpoint (LOCF) in patients receiving liraglutide than in those receiving dulaglutide (p=0·012); amylase concentrations did not differ between groups (table 3). The percentage of patients with treatment-emergent pancreatic enzyme concentrations of three times the upper limit of normal or higher was low, and similar between treatment groups (table 3). Mean serum calcitonin concentrations did not change during the study in either group (mean change –0·01 pmol/L [SD 0·45] in dulaglutide group and 0·05 pmol/L (0·45) in liraglutide group; p=0·11). One patient receiving liraglutide was diagnosed with a treatment-emergent papillary thyroid carcinoma. There were no reports of C-cell hyperplasia or medullary thyroid carcinoma.

There was one cardiovascular event of myocardial infarction, confirmed by adjudication, in the liraglutide group. We noted similar changes in both systolic and diastolic blood pressure at week 26 (table 3). Increases in mean heart rate occurred in both groups, with no significant between-group difference (table 3). We noted no between-group differences in lipid parameters or ECG assessments (appendix).

Three (1%) patients receiving dulaglutide developed treatment-emergent antibodies to dulaglutide (liraglutide antibodies were not assessed; table 3). None of these patients had hypersensitivity events. The frequency of hypersensitivity events across groups was very low and much the same (data not shown), and few patients had injection-site reactions (one patient receiving dulaglutide *vs* two receiving liraglutide).

For patient-reported outcomes, both groups had significant improvements in impact of weight on self-perception and the European quality of life 5 dimensions (visual analogue scale), with no between-group differences (data not shown). Patients in the dulaglutide group had significant improvements from baseline in ability to perform physical activities of daily living (p=0·014) and European quality of life 5 dimensions UK population score (p=0·031); patients in the liraglutide group did not differ in these measures

between baseline and follow-up, and between-group differences were not significant for either measure (data not shown).

Discussion

Findings from the AWARD-6 trial show that once-weekly dulaglutide is non-inferior to once-daily liraglutide. Both treatment groups had robust HbA_{1c} reductions, with most patients achieving the HbA_{1c} target of less than 7·0% (<53 mmol/mol) recommended by the European Association for the Study of Diabetes and American Diabetes Association.[7] Additionally, both groups had small reductions in bodyweight, with patients receiving liraglutide losing significantly more weight than patients receiving dulaglutide. Safety and tolerability profiles of the two GLP-1 receptor agonists were very similar.

For both groups, our study findings are consistent with those reported in previous studies (panel). In previous studies of dulaglutide (1·5 mg), with primary endpoints at 26–52 weeks' follow-up and baseline HbA_{1c} of 7·6–8·1% (60–65 mmol/mol), investigators reported HbA_{1c} reductions of –0·78% to –1·51% (–8·5 to –16·5 mmol/mol), with 61–78% of patients achieving an HbA_{1c} of less than 7·0% (<53 mmol/mol).[13,18,19] Previous studies of liraglutide (1·8 mg), with mainly 26-week treatment durations and baseline HbA_{1c} ranging from 8·2% to 8·6% (66–70 mmol/mol), have shown HbA_{1c} reductions of –0·99% to –1·50% (–10·8 to –16·4 mmol/mol) with 42–60% of patients achieving an HbA_{1c} of less than 7·0% (<53 mmol/mol).[12,14,27–30] Although other drugs with weekly dosing have not shown non-inferiority against once-daily liraglutide, our findings suggest that dulaglutide 1·5 mg is non-inferior to liraglutide 1·8 mg.

AWARD-6 met the primary hypothesis of non-inferiority with a prespecified non-inferiority margin of 0·4% because the upper bound of the 95% CI for the treatment difference, at 0·07%, was less than 0·4%. Although our study was powered to show non-inferiority with a 0·4% margin, the upper bound was less than that required to show non-inferiority for a margin of 0·3% or even 0·25%; therefore, the study findings would have shown non-inferiority if these margins had been used instead. For a given level of power, treatment effect, and measurement variability, a smaller margin requires a larger sample size. The two previous studies of GLP-1 receptor agonists comparing once-weekly with once-daily dosing, DURATION-6 and HARMONY-7 (comparing liraglutide with exenatide once-weekly and with albiglutide, respectively) had non-inferiority margins of 0·25% and 0·30%, respectively, with sample sizes of 911 and 812 patients, compared with 599 patients in AWARD-6.[12,14] Findings from these studies showed between-treatment group differences of 0·21% (95% CI 0·08–0·33) for DURATION-6 and 0·21% (0·08–0·34) for HARMONY-7, which did not show non-inferiority to liraglutide. Although both studies had an upper bound of the 95% CI that was less than 0·4%, whether these studies would have met non-inferiority with a 0·4% margin cannot be concluded because the sample size for this theoretical experiment would have been much smaller, probably resulting in a wider CI. Possible explanations for differences in the study outcomes between AWARD-6 and these studies might result from differences in efficacy of the once-weekly GLP-1 receptor agonists used in these studies (possibly as a result of differential dose selection based on acceptable efficacy with favourable tolerability and drug-specific properties), or other study-specific differences (eg, background therapy and baseline HbA_{1c}).[31]

In AWARD-6, we noted small weight reductions in both groups, consistent with findings from previous studies. In a recent study of treatment add-on to metformin, patients receiving dulaglutide 1·5 mg had a weight reduction of 3·0 kg over 52 weeks, which notably was observed by 26 weeks in the previous study,[19] whereas patients receiving liraglutide 1·8 mg in combination with metformin had weight reductions of 2·8 kg and 3·3 kg in two 26-week studies.[30,32] We noted a mean weight reduction of 3·6 kg in the liraglutide group, which was greater than that in the dulaglutide group (2·9 kg reduction). The reason for this difference is unclear, although might be related to differences in mechanism of action with respect to central and peripheral activity.[5,33] The incidence, persistence, and severity of gastrointestinal events were much the same between groups. Patient-reported outcomes assessing the effect of weight on self-perception and activities of daily living were similar between groups, as was treatment compliance.

Panel: Research in context

Systematic review

We searched PubMed on April 10, 2013, with the terms "liraglutide", "exenatide", "albiglutide", and "randomized clinical trial" with no date or trial duration restrictions. Non-English references were excluded. We identified two trials in which a once-weekly glucagon receptor agonist drug was directly compared with once-daily liraglutide; neither met non-inferiority (DURATION-6 and HARMONY 7).[12,14]

Interpretation

Our findings suggest that once-weekly administration of dulaglutide 1·5 mg is non-inferior to once-daily administration of liraglutide 1·8 mg for glycaemic control. Patients in both treatment groups lost weight, with patients in the liraglutide group losing 0·71 kg more than did those in the dulaglutide group. Dulaglutide and liraglutide had a similar safety and tolerability profile with low rates of hypoglycaemia. To our knowledge, these phase 3 study findings are the first to show non-inferiority of a once-weekly GLP-1 receptor agonist to once-daily liraglutide. These findings will help to inform treatment decisions for patients with type 2 diabetes.

The safety and tolerability profiles were similar for dulaglutide and liraglutide and are consistent with the known class effects. Few patients had hypoglycaemia. Injection-site reactions were uncommon in both groups. We recorded no cases of pancreatic cancer or adjudicated pancreatitis. The importance of the difference in lipase concentrations between groups is unclear and has not been reported previously in head-to-head studies of liraglutide with other GLP-1 receptor agonists.[12,14,27] However, the increases that we noted in pancreatic enzyme concentrations were generally similar between groups and were not unexpected on the basis of previous reports.[6,10,34] These elevations were not predictive of pancreatitis, and we noted no clinical consequences of these elevations. Changes in vital signs were similar between groups and consistent with findings from previous studies of GLP-1 receptor agonists.[6,32,35]

Limitations of our study include the open-label design, which could have affected physicians' and patients' behaviour. However, placebo pens for liraglutide were not commercially available. The length of the study was fairly short in view of the chronic nature of type 2 diabetes, but it was long enough for each treatment to reach steady state and the treatment effect to be represented in the primary outcome of HbA_{1c}.

In conclusion, findings from the AWARD-6 study lend support to the efficacy of the GLP-1 receptor agonist drugs dulaglutide and liraglutide for control of hyperglycaemia in type 2 diabetes. With once-weekly dulaglutide 1·5 mg, patients administered substantially fewer injections and yet still achieved similar glycaemic benefits. Long-term, once-weekly drugs might improve compliance compared with more frequently administered regimens, but this notion will require further assessment.

Contributors

KMD and JLF designed the trial. STP, TF, and JGGG were trial investigators and participated in data collection. JLF was responsible for medical oversight during the trial. CA was responsible for the statistical considerations in the analysis and trial design. All authors participated in critical reviewing and interpreting the data for the manuscript. All authors approved the final version of the manuscript and take full responsibility for the content. KMD and JLF had final responsibility for the decision to submit for publication.

Declaration of interests

KMD reports consulting and advisory board activities with Eli Lilly and Company, and research support from Novo Nordisk. STP has received honoraria for lectures and research funding from Eli Lilly and Company. TF has received speaker and advisory fees from Eli Lilly and Company. JGGG has received funding for activities at organisation's research site from Eli Lilly and Company. CA, WS, and JLF are employees of Eli Lilly and Company.

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References

1 DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005; **28:** 1092–100.

2 Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; **368:** 1696–705.

3 Drucker DJ, Buse JB, Taylor K, et al, for the DURATION-1 Study Group. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* 2008; **372:** 1240–50.

4 Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol* 2012; **8:** 728–42.

5 Lund A, Knop FK, Vilsboll T. Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes: differences and similarities. *Eur J Intern Med* 2014; **25:** 407–14.

6 Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2011; **96:** 1301–10.

7 Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; **35:** 1364–79.

8 Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in Basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 2011; **154:** 103–12.

9 Sanofi-Aventis. Summary of product characteristics (Lyxumia). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002445/WC500140401.pdf (accessed March 12, 2014).

10 DeVries JH, Bain SC, Rodbard HW, et al. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1c targets. *Diabetes Care* 2012; **35:** 1446–54.

11 Bolli GB, Munteanu M, Dotsenko S, et al. Efficacy and safety of lixisenatide once daily *vs* placebo in people with type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). *Diabet Med* 2013; **31:** 176–84.

12 Pratley RE, Nauck MA, Barnett AH, et al, for the HARMONY 7 study group. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. *Lancet Diabetes Endocrinol* 2014; **2:** 289–97.

13 Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added on to pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care* 2014; published online May 30. DOI:10.2337/dc13-2760.

14 Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet* 2013; **381:** 117–24.

15 Barrington P, Chien JY, Tibaldi F, Showalter HD, Schneck K, Ellis B. LY2189265, a long-acting glucagon-like peptide-1 analogue, showed a dose-dependent effect on insulin secretion in healthy subjects. *Diabetes Obes Metab* 2011; **13:** 434–38.

16 Glaesner W, Vick AM, Millican R, et al. Engineering and characterization of the long-acting glucagon-like peptide-1 analogue LY2189265, an Fc fusion protein. *Diabetes Metab Res Rev* 2010; **26:** 287–96.

17 Barrington P, Chien JY, Showalter HD, et al. A 5-week study of the pharmacokinetics and pharmacodynamics of LY2189265, a novel, long-acting glucagon-like peptide-1 analogue, in patients with type 2 diabetes. *Diabetes Obes Metab* 2011; **13:** 426–33.

18 Umpierrez GE, Povedano ST, Manghi FP, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy *vs* metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). *Diabetes Care* 2014; published online May 19. DOI:10.2337/dc13-2759.

19 Nauck M, Weinstock R, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and Safety of Dulaglutide Versus Sitagliptin After 52 Weeks in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-5). *Diabetes Care* 2014; published online April 17. DOI:10.2337/dc13-2761.

20 World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 1997; **277:** 925–26.

21 Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005; **28:** 1245–49.

22 Hayes RP, Nelson DR, Meldahl ML, Curtis BH. Ability to perform daily physical activities in individuals with type 2 diabetes and moderate obesity: a preliminary validation of the Impact of Weight on Activities of Daily Living Questionnaire. *Diabetes Technol Ther* 2011; **13:** 705–12.

23 Hayes RP, Schultz EM, Naegeli AN, Curtis BH. Test-retest, responsiveness, and minimal important change of the ability to perform physical activities of daily living questionnaire in individuals with type 2 diabetes and obesity. *Diabetes Technol Ther* 2012; **14:** 1118–25.

24 Brooks R, Rabin R, deCharro F. The measurement and valuation of health status using EQ-5D: a European Perspective. Evidence from the EuroQol BIOMED Research Programme. Dodrecht, Boston, London: Kluwer Academic Publishers, 2003.

25 Dmitrienko A, Tamhane AC, Wang X, Chen X. Stepwise gatekeeping procedures in clinical trial applications. *Biom J* 2006; **48:** 984–91.

26 Dmitrienko A, Tamhane AC, Wiens BL. General multistage gatekeeping procedures. *Biom J* 2008; **50:** 667–77.

27 Buse JB, Rosenstock J, Sesti G, et al, for the LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 2009; **374:** 39–47.

28 Zinman B, Gerich J, Buse JB, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care* 2009; **32:** 1224–30.

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

30 Nauck M, Frid A, Hermansen K, et al. 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* 2009; **32:** 84–90.

31 Garber A. GLP-1 receptor agonists: why is once weekly inferior to once daily? *Lancet Diabetes Endocrinol* 2014; **2:** 266–67.

32 Pratley RE, Nauck M, Bailey T, et al, for the 1860-LIRA-DPP-4 Study Group. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* 2010; **375:** 1447–56.

33 Baggio LL, Huang Q, Brown TJ, Drucker DJ. A recombinant human glucagon-like peptide (GLP)-1-albumin protein (albugon) mimics peptidergic activation of GLP-1 receptor-dependent pathways coupled with satiety, gastrointestinal motility, and glucose homeostasis. *Diabetes* 2004; **53:** 2492–500.

34 Steinberg W, DeVries JH, Wadden TA, Jensen CB, Svendsen CB, Rosenstock J. Longitudinal monitoring of lipase and amylase in adults with type 2 diabetes and obesity: evidence from two phase 3 randomized clinical trials with the once-daily GLP-1 analog liraglutide [poster presentation at Digestive Disease Week 2012]. *Gastroenterology* 2012; **142** (suppl 1)**:** S850–51.

35 Ferdinand K, Calhoun D, Lonn E, et al. Long-term effects of dulaglutide, a novel GLP-1 agonist, on ambulatory blood pressure and heart rate in patients with type 2 diabetes. Abstract LB-OR-04. *J Clin Hypertension* 2012; **14:** 488.