Metabolic and functional evaluation of diabetic cardiomyopathy using MR Spectroscopy and MR Imaging

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Chapter 8

Efficacy of Liraglutide on Glycemic Endpoints in People of Western European and South Asian Descent with T2DM using Multiple Daily Insulin Injections: Results of the MAGNA VICTORIA Studies

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Abstract

Aims

Data on the effect of liraglutide on glycemic endpoints in people with T2DM using multiple daily insulin injections (MDI) are scarce, especially in the context of ethnicity.

Methods

This is a secondary analysis of the placebo-controlled randomized clinical "MAGNA VICTORIA" trials in Western European (WE) and South Asian (SA) people with T2DM. Participants had inadequate glycemic control despite using metformin and/or sulfonylurea derivatives and/or insulin. Participants were assigned to liraglutide (1.8 mg) or placebo for 6 months, in addition to standard care. The primary endpoint number of participants reaching target HbA1c was compared for liraglutide versus placebo in the complete dataset and MDI-treated participants using Chi-square test. Liraglutide's efficacy in WE and SA was compared using a generalized linear model.

Results

Forty-five subjects were randomized to liraglutide and 51 to placebo. In each group, one participant did not complete the study. Liraglutide-treated patients reached target HbA1c more frequently: 23/45 (51%) vs 11/51 (22%), relative probability 2.4 (1.3–4.3), p = 0.002. Subgroup analysis in 43 MDI participants showed that the proportion reaching target HbA1c using liraglutide was significantly higher than in placebo: 9/22 (41%) vs 1/21 (5%), p = 0.005. There was no difference between WE and SA in terms of liraglutide efficacy (p = 0.18).

Conclusions

Liraglutide treatment resulted in increased chance of reaching target HbA1c as compared to placebo. Liraglutide efficacy was sustained in participants using MDI regimens and those of SA descent. Liraglutide should be considered for T2DM people with inadequate glycemic control despite MDI.

Introduction

The primary goal in T2DM management is the prevention of diabetes-associated complications. To maximally reduce complication risk, for most patients, a target HbA1c of ≤ 7.0% (53 mmol/mol) is advocated[1]. The chance of reaching this glycemic goal with lifestyle and pharmaceutical interventions depends, in part, on the severity of underlying pathophysiologic features of T2DM: insulin resistance and beta cell deficiency[2, 3]. Dependent on severity and relative contribution of insulin resistance and beta cell deficiency, therapy with insulin is warranted in order to restore glycemic control.

In addition to individual patient characteristics (i.e., BMI, age, auto-antibodies and genetic factors[3]) related to insulin resistance and beta cell deficiency, ethnicity also contributes to T2DM heterogeneity. The population of Surinamese Hindustani living in the Netherlands is an example of such an ethnic population with a specific T2DM disease course[4]. Surinamese Hindustani are South Asian (SA) as they have their ancestry from the Indian subcontinent South Asia[5]. When compared to native Dutch Western European (WE) people, SA have shown higher rates of insulin resistance as well as poorer beta cell function adjusted for adiposity, family history and insulin sensitivity, as compared to other ethnicities[6-9]. As such SA develop T2DM at younger age, and also have increased diabetes-associated complication burden and mortality[3, 10].

In patients with the most severe insulin resistance and beta cell deficiency, such as South Asians, treatment with multiple daily insulin injections (MDI, defined as: premix or a combination of basal insulin and prandial/bolus insulin) is often needed to restore glycemic control. MDI is often considered as a last resort in T2DM management. However, MDI treatment is often not successful with, at best 50% of those patients reaching target HbA1c[11]. The reasons for this are probably related to some of the drawbacks of intensive insulin treatment: increase in body weight and risk of hypoglycemia, and its blunted efficacy in the setting of severe insulin resistance[12]. So, to combat the high complication rate in the most severely affected T2DM cases[3],

such as South Asians, studies are needed on how to improve glycemic control in patients already on MDI regimen though still have their HbA1c above target.

Liraglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) that improves glycemia by reducing appetite, promoting glucose-stimulated insulin secretion and reducing glucagon secretion. Its favorable effects, as compared to insulin, include lower hypoglycemia risk, body weight reduction and reduction of major adverse cardiovascular events[13]. Although a limited number of studies has suggested beneficial effects on HbA1c, body weight and hypoglycemia risk with addition of liraglutide to an MDI regimen[14, 15], currently, the ADA/EASD T2DM management guideline does not advocate addition of GLP-1RA to an MDI regimen[1]. One of the limitations of the studies with liraglutide in MDI patients so far, is that they were performed in patients of WE descent who were, in general, morbidly obese. Thereby these studies potentially represent a different T2DM phenotype than the phenotype of most SA patients that have relatively low BMI and worse beta cell function[3]. In light of the fact that GLP-1RA efficacy is, in part, dependent on residual beta cell function[16, 17], it is important to include MDI patients with lower BMI and of SA descent in clinical trials.

Therefore, the purpose of this study was to investigate whether liraglutide added to an MDI regimen in people with T2DM of SA and WE descent improves glycemic control.

Methods

Study design and participants

This is a secondary pooled analysis of the MAGNA VICTORIA studies (MAGNetic resonance Assessment of VICTOza efficacy in the Regression of cardiovascular dysfunction In type 2 diAbetes mellitus) in Dutch WE (NCT01761318)[18] and Dutch SA (NCT02660047)[19, 20] patients with T2DM. The primary goal of these 26-week, randomized, double-blind, placebo-controlled, single-center studies was to assess the effect of liraglutide on cardiac function. Inclusion criteria for WE participants were: age 18–69 years, BMI ≥ 25 kg/m^2 and HbA1c between 7.0 and 10.0% (53–86 mmol/mol) while using metformin and/or sulfonylurea derivative and/or insulin. For

SA subjects, inclusion criteria were: age 18–74 years, BMI ≥ 23 kg/m^2 and HbA1c between 6.5 and 11.0% (47.5–96.4 mmol/mol) while the use of metformin, sulfonylurea derivative and insulin was optional. Inclusion criteria for SA were broadened to enable sufficient inclusion rate. Exclusion criteria for WE and SA participants were: use of DPP4-inhibitor, GLP-1RA, previous pancreatitis, gastric bypass surgery, pregnancy or lactation and severe hepatic or renal disease. In WE participants, all patients with history of or signs/symptoms of heart disease were excluded. In SA participants, patients with NYHA class III–IV heart failure, or acute coronary or cerebrovascular accident < 30 days prior to the study were excluded. The trials were approved by the local ethics committee and performed in accordance with the principles of the Declaration of Helsinki (as revised in Brazil 2013). Written informed consent was obtained from all participants before study. The trial was conducted at the Leiden University Medical Center (LUMC), Leiden, the Netherlands.

Randomization

In both MAGNA VICTORIA studies, the included participants were randomly assigned to liraglutide (Victoza, Novo Nordisk A/S, Bagsværd, Denmark) or placebo (provided by Novo Nordisk A/S, Bagsværd, Denmark) with 1:1 stratification for sex and insulin use and 4 participants per block. The institutional pharmacist executed randomization.

Glycemic management

Sulfonylurea derivative and basal insulin dose reductions were considered at study start if fasting plasma glucose (PG) was < 90 mg/dL (5.0 mmol/L). Premix insulin and mealtime bolus insulin dose reductions were reduced by 50% when fasting PG was < 180 mg/dL (10 mmol/L) and pre-prandial PG was < 270 mg/dL (15 mmol/L). In the first week, the study drug was initiated at 0.6 mg once daily, and if tolerated, uptitrated to 1.2 mg and 1.8 mg in the second and third week, respectively. To prevent hypoglycemia in these weeks, safe targets were set: fasting PG 90–180 mg/dL (5.0–10.0 mmol/L) and pre-prandial PG < 270 mg/dL (15 mmol/L). An ambulant glucose meter (A. Menarini Diagnostics, Florence, Italy) was provided to participants. Participants using oral blood glucose-lowering drugs were instructed to measure

fasting PG once weekly, and additionally in case of hypoglycemic symptoms as instructed by the investigators. Participants using basal insulin were advised to measure fasting PG daily and in case of hypoglycemic episodes, while those using premix and basal-bolus regimen to measure pre-bolus PG twice and four times daily, respectively. From week three on, glycemic management was practiced in accordance with practice guidelines targeting fasting PG of 81–144 mg/dL (4.5–8.0 mmol/L) and pre-prandial PG < 180 mg/dL (10.0 mmol/L). At week 12, concomitant treatment with sulfonylurea derivative and insulin was guided further in an attempt to reach target HbA1c ≤ 7.0% (≤ 53 mmol/mol).

Data collection

Hypoglycemic episodes and PG as reported in the participants' diabetes diaries as well as drug dosage were assessed by weekly telephone calls, and monthly visits to the research clinic. These contact moments were also used to provide individualized titration of sulfonylurea derivative and insulin. At the end of both studies, ambulant blood glucose meters and diaries were collected. Using these data, hypoglycemic episodes were scored. To calculate daily insulin use, the average of the 2 weeks prior was used. Premix insulin dosage was calculated back to subdivide in basal and bolus insulin. HbA1c was measured at start, week 12 and at the end of the studies as described previously[18,20] using ion-exchange high-performance liquid chromatography (Tosoh G8, Sysmex Nederland B.V., Etten-Leur, the Netherlands) in majority of cases, and corrected for if measured otherwise.

Study endpoints

We previously reported the primary endpoints of the MAGNA VICTORIA study that involved left ventricular diastolic and systolic function[18, 19]. In these publications, body weight and HbA1c were reported. The current analysis focusses on hypoglycemic episodes and proportion reaching target HbA1c of 7.0% or below (≤ 53 mmol/L). Hypoglycemic events were scored as follows: severe hypoglycemia (requiring assistance from another individual to actively administer carbohydrates or glucagon, irrespective of availability of glucose level), documented moderate/grade 2 hypoglycemia (PG ≤ 54 mg/dL (3.0 mmol/L) irrespective of symptoms), documented

mild/grade 1 hypoglycemia (PG 55–70 mg/dL (3.1–3.9 mmol/L), irrespective of symptoms), probable symptomatic hypoglycemia (symptoms of hypoglycemia not accompanied by determination of glucose level) and relative hypoglycemia (symptoms of hypoglycemia with a measured glucose concentration ≥ 71 mg/dL (4.0 mmol/L). Confirmed hypoglycemic episode was defined as severe, grade 2 or grade 1 documented episode.

Statistics

Sample size of both studies was calculated for the primary endpoints related to left ventricular function. Both studies aimed to include 50 participants. Data are shown as mean ± SD when normally distributed, or as median (interquartile range) when not normally distributed. Proportion of participants that reached target HbA1c (without hypoglycemia) and proportion without confirmed hypoglycemia were compared with chi-square. Generalized linear model was used to compare liraglutide efficacy between SA and WE. Hypoglycemic rates (mean ± SD) were compared using unpaired t test. Between-group changes (mean, 95% confidence interval) in body weight and HbA1c were analyzed using ANCOVA. Statistical analyses were performed using SPSS version 25 for Windows (IBM Corporation, Chicago, IL). P value < 0.05 was considered statistically significant.

Role of the funding source

The MAGNA VICTORIA studies were investigator-initiated. Novo Nordisk A/S (Bagsværd, Denmark) funded both studies. The study sponsor was not involved in the design of the MAGNA VICTORIA studies or the present secondary pooled analysis, nor in the collection, analysis and interpretation of data; writing of the report; or the decision to submit the report for publication.

Results

Study population

Participants in the MAGNA VICTORIA studies were enrolled between December 2013 and 2016. In total, 50 WE and 47 SA participants were enrolled. One

participant in the liraglutide group withdrew consent before having received study drug and was not included in intention-to-treat analysis, and one subject was withdrawn from the study because of frequent hypoglycemic events (on further examination the diagnosis diabetes mellitus type 1 was made). In the placebo group, one participant was lost to follow-up. As a result, intention-to-treat analysis was performed in 96 participants. Baseline characteristics are shown in Table 1. Overall, the liraglutide group had a higher proportion of participants with diabetic retinopathy and neuropathy whereas nephropathy at baseline occurred more often in the placebo group. HbA1c values at baseline were comparable between groups, except that participants randomized to liraglutide had higher BMI.

Table 2 shows baseline characteristics for WE and SA populations separately. SA population had 7 years longer diabetes duration despite being 5 years younger than WE. Another difference observed was the lower BMI of SA, whereas a higher proportion was treated with MDI (30/47 vs 13/49). HbA1c was comparable between SA and WE. Furthermore, rates of retinopathy and macrovascular disease were higher in SA compared to WE. Baseline characteristics of participants using MDI regimens are displayed in Table 3. MDI subgroup had mean diabetes duration of 20 years and BMI of 30 kg/m^2. Despite the daily insulin use of 90 IE, HbA1c at baseline was 8.4% (68 mmol/mol) in liraglutide and 8.8% (72 mmol/mol) in placebo group.

Study drug and concomitant drug use

In liraglutide-treated group, two subjects were on 0.6 mg during most days during the study; six on 1.2 mg and 37 on 1.8 mg. Study drug dose reductions were applied in twelve participants, and study drug up-titration was delayed in nine. In the placebo group, all but one participant used 1.8 mg (one participant used 1.2 mg) and two participants required a study drug dose reduction due to adverse effects. In four participants, there was a delayed up-titration of study drug. Almost all participants used metformin and the mean dose was not adjusted during the study. Sulfonylurea derivatives were stopped in two participants within the liraglutide group. In the placebo group, six subjects were started on a sulfonylurea derivative, and in three participants, the sulfonylurea derivative dose was increased. In the liraglutide group, three participants using basal-bolus and one participant using a premix regimen were

switched to basal insulin, and one participant using premix insulin was switched to a basal-bolus regimen. In the placebo group, two participants were started on basal insulin and two participants were intensified from basal to basal-bolus insulin. In the other participants of the placebo group who used insulin, only dose changes were applied. The insulin dose decreased from (mean ± SD) 74 ± 40 to 60 ± 46 IE/day in the liraglutide group. In placebo-treated participants, insulin dose decreased from 68 ± 45 to 66 ± 37 IE/day. The between-group difference (mean estimated treatment effect) was 14.3 IE/day decrease in liraglutide versus placebo (95% CI from − 26.6 to − 2.0; p = 0.024).

Table 1. Baseline characteristics

	Liraglutide (n=45)	Placebo (n=51)
Demographics		
Age, years	58 (9)	57 (9)
Men, n (%)	22 (49)	26 (51)
Ethnicity		
Western European, n (%)	23 (51)	26 (51)
South Asian, n (%)	22 (49)	25 (49)
Diabetes duration, years	15 (9)	14 (9)
Diabetic retinopathy, n (%)	17 (38)	13 (26)
Diabetic nephropathy, n (%)	5 (11)	18 (35)
Diabetic neuropathy, n (%)	19 (42)	12 (24)
Macrovascular disease†, n (%)	9 (20)	6 (12)
Clinical parameters		
Weight, kg	90.4 (14.9)	86.3 (15.2)
BMI, kg/m^2	31.5 (4.2)	30.1 (4.0)
HbA1c, %	8.2 (1.0)	8.3 (1.0)
HbA1c, mmol/mol	65.7 (10.6)	67.5 (11.4)
Smoking history		
Never smoked, n (%)	24 (53.3)	28 (54.9)
Current smoker, n (%)	6 (13.3)	10 (19.6)
Ex-smoker, n (%)	15 (33.3)	13 (25.5)

Data are presented as mean (SD) unless specified otherwise. †in the Western European cohort coronary artery disease was excluded, one patient had cerebrovascular disease and one had peripheral artery disease. In the South Asian cohort coronary artery disease was not amongst exclusion criteria.

Table 2. Baseline characteristics specified by ethnicity

	WE (n=49)	SA (n=47)
Demographics		
Age, years	60 (7)	55 (10)
Men, n (%)	29 (59)	19 (40)
Diabetes duration, years	11 (7)	18 (10)
Diabetic retinopathy, n (%)	6 (12)	24 (51)
Diabetic nephropathy, n (%)	13 (27)	10 (20)
Diabetic neuropathy, n (%)	17 (35)	14 (30)
Macrovascular disease, n (%)	2 (4)	13 (28)
Clinical parameters		
Weight, kg	96 (13)	80 (12)
BMI, kg/m^2	32 (4)	29 (4)
HbA1c, %	8.2 (1.0)	8.4 (1.0)
HbA1c, mmol/mol	66 (11)	68 (11)
Concomitant glucose lowering drugs		
Metformin use, n (%)	49 (100)	45 (96)
Metformin dosage, g/day	2.0 (0.6)	1.7 (0.6)
Sulfonylurea derivative, n (%)	14 (29)	8 (17)
Insulin use, n (%)	32 (65)	36 (77)
Insulin, IE/day	69 (52)	72 (32)
Basal insulin, n (%)	*19 (59)*	*6 (17)*
Premix insulin, n (%)	*1 (3)*	*8 (22)*
Basal-bolus insulin, n (%)	*12 (38)*	*22 (61)*

Data are presented as mean (SD) unless specified otherwise. Abbreviations: SA = South Asians; WE = Western Europeans.

Table 3. Baseline characteristics and glycemic control in participants using multiple daily insulin injections

	Liraglutide (n=22)	Placebo (n=21)	Mean Δ (SE)	
Age, years	59 (10)	56 (8)	3 (3)	
Men, n (%)	10 (46)	10 (48)	NA	
Ethnicity				
WE, n (%)	7 (32)	6 (29)	NA	
SA, n (%)	15 (68)	15 (71)		
Weight, kg	86 (16)	85 (15)	1 (5)	
BMI, kg/m^2	30 (4)	30 (4)	0 (1)	
Diabetes duration, years	20 (8)	20 (9)	1 (3)	
Insulin, IE/day	91 (35)	89 (47)	2 (13)	
HbA1c, %	8.4 (0.8)	8.8 (1.1)	-0.4 (0.3)	
HbA1c, mmol/mol	68 (8.2)	72 (12)	-5 (3)	
			Relative probability (95% CI)	**p-value**
HbA1c within target, n (%)†	9 (41)	1 (5)	8.2 (1.2 to 62.5)	0.005*
Absence of confirmed hypoglycemia, n (%)‡	9 (41)	7 (33)	1.3 (0.6 to 2.7)	0.61
HbA1c within target without confirmed hypoglycemia, n (%)	2 (9)	0	NA	NA

Data are presented as mean (SD) unless specified otherwise. †in accordance with standards of diabetes care, target HbA1c was set ≤ 7.0% (≤ 53 mmol/mol). ‡Confirmed hypoglycemia was defined as grade 2 or grade 1 hypoglycemia that occurred during the 6-month trial period. *p<0.05. Abbreviations: SA = South Asian; WE = Western European.

Overview trial results

Body weight decrease was significantly higher in liraglutide group: mean treatment effect − 4.0 kg (95% CI: − 5.2 to − 2.7 kg, p < 0.001) with BMI difference

between liraglutide and placebo − 1.4 kg/m2 (95% CI: − 1.9 to − 1.0 kg/m^2, p < 0.001). The mean differences in HbA1c decline between liraglutide (from 8.2 to 7.2%, 66–56 mmol/mol) and placebo (from 8.3 to 7.7%, 68–60 mmol/mol) was − 0.3% (− 3.6 mmol/mol) in favor of liraglutide, but did not reach statistical significance (p = 0.06). Table 4 shows that the relative probability to reach target HbA1c was 2.4 times higher in liraglutide-treated participants (51% vs 22%), and that 31% in the liraglutide group reached that target without a confirmed (grade 1 or grade 2) hypoglycemic episode, compared to 14% in the placebo group. Data on hypoglycemic episodes are presented in Table 5. Overall, hypoglycemic rate was slightly lower in liraglutide-treated participants, but was not statistically different from the placebo group. Figure 1 represents an overview of the trial results, including subgroups described below.

MDI participants

Table 3 shows the results for the 43 participants using MDI. At baseline, liraglutide group used 45 IE/day as basal insulin and 46 IE/day as bolus, whereas in placebo basal insulin use was 43 IE/day with 47 IE/day as bolus. In liraglutide group, total daily insulin use decreased with mean 16 ± 34 IE/day and decreased with 1 IE/day in placebo group (between-group difference 14 IE/day with 95% CI − 5 to 34 IE/day, p = 0.14). In participants using liraglutide nine (41%) reached target HbA1c whereas only one participant (5%) did so in the placebo group, resulting in a relative probability of 8.2 (95% CI from 1.2 to 62.5, p = 0.005).

South Asian participants

Table 6 displays the results for ethnic subgroups. In both WE and SA, the proportion reaching target HbA1c was significantly greater with liraglutide than placebo (relative probabilities: 2.1 for WE vs 2.8 for SA, p = 0.03), without a significant between-group difference (p = 0.18). All other endpoints did not reach statistical significance in the subgroups, though showed similar trends for WE and SA (see table 7 for hypoglycemic rate).

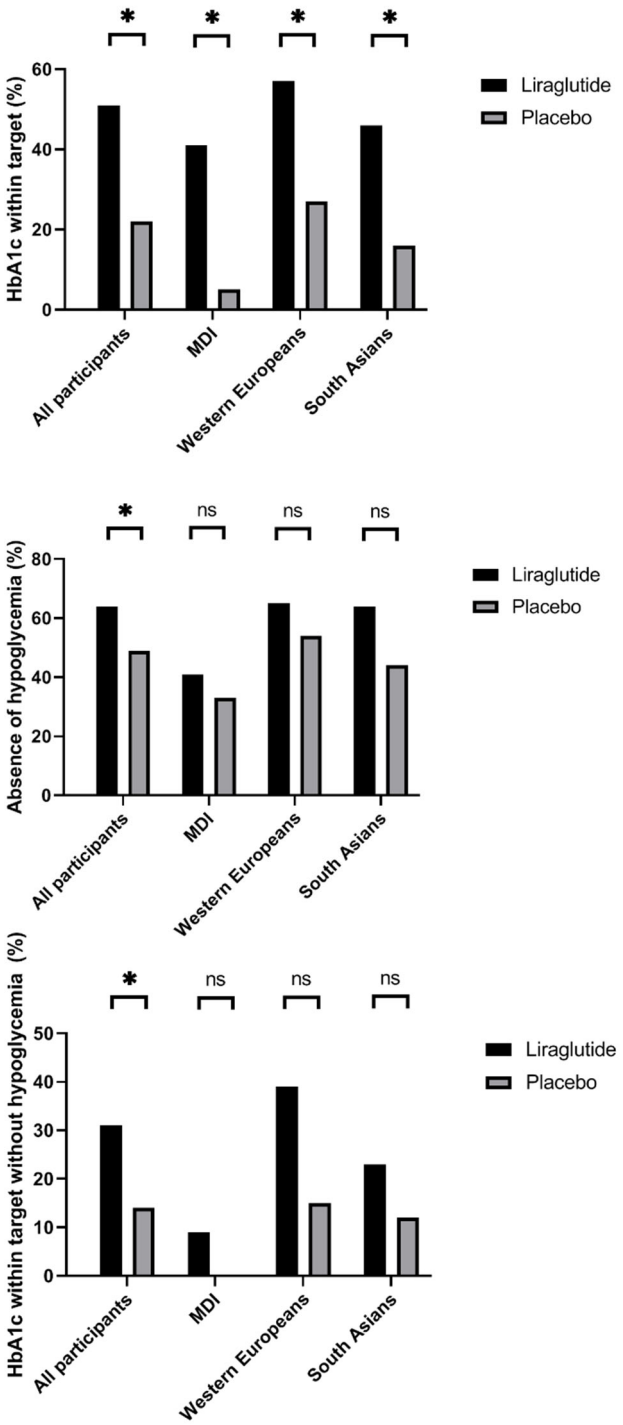

Figure 1. Glycemic targets in the whole cohort, in participants using MDI, and specified by ethnicity. Upper panel displays the proportion of patients reaching target HbA1c ≤ 7.0% (53 mmol/mol) at week 26. The middle panel shows the proportion of patients that had no episode of grade 1 or grade 2 confirmed hypoglycemia during the study period. The lower panel indicates proportion of patients that met HbA1c target level and had no confirmed hypoglycemic episode during study period. * $p<0.05$; Abbreviations: NS = not significant; MDI = multiple daily insulin injection.

Table 4. Glycemic control in complete dataset

	Liraglutide (n=44)	Placebo (n=50)	Relative probability (95% CI)	p-value
HbA1c within target†	23 (51)	11 (22)	2.4 (1.3 to 4.3)	0.002*
Absence of confirmed hypoglycemia‡	29 (64)	25 (49)	1.3 (0.9 to 1.9)	0.13
HbA1c within target without confirmed hypoglycemia	14 (31)	7 (14)	2.2 (1.0 to 5.0)	0.045*

Data are presented as n (%). †in accordance with standards of diabetes care, target HbA1c was set ≤ 7.0% (≤ 53 mmol/mol). ‡Confirmed hypoglycemia was defined as grade 2 or grade 1 hypoglycemia that occurred during the 6-month trial period. *p<0.05.

Table 5. Hypoglycemia risk in complete dataset

	Liraglutide (n=44)	Placebo (n=50)	Mean difference (95% CI)	p-value
Total hypoglycemic rate, mean/participants (SD)	1.8 (3.3)	2.7 (3.6)	-0.9 (-2.3 to 0.5)	0.22
Total confirmed hypoglycemic rate†, mean/participants (SD)	1.6 (3.1)	2.2 (3.3)	-0.6 (-1.9 to 0.6)	0.33
Severe hypoglycemia, n	0	0	NA	NA
Grade 2 hypoglycemia, mean/participants (SD)	0.4 (0.9)	0.3 (0.8)	0.0 (-0.3 to 0.4)	0.82
Grade 1 hypoglycemia, mean/participants (SD)	1.2 (2.6)	1.9 (2.8)	-0.7 (-1.8 to 0.4)	0.22
Relative hypoglycemia, mean/participants (SD)	0.1 (0.4)	0.2 (0.9)	-0.1 (-0.4 to 0.1)	0.21
Probable hypoglycemia, mean/participants (SD)	0.2 (0.4)	0.2 (0.7)	-0.1 (-0.4 to 0.2)	0.58

†Confirmed hypoglycemia was defined as grade 2 or grade 1 hypoglycemia that occurred during the 6-month trial period.

Table 6. Glycemic control specified by ethnicity

	Liraglutide		Placebo		Relative probability (95% CI)		p-value	
	WE (n=23)	SA (n=22)	WE (n=26)	SA (n=25)	WE	SA	WE	SA
HbA1c within target, n (%)†	13 (57)	10 (46)	7 (27)	4 (16)	2.1 (1.0 to 4.3)	2.8 (1.0 to 7.8)	0.03*	0.03*
Absence of confirmed hypoglycemia, n (%)‡	15 (65)	14 (64)	14 (54)	11 (44)	1.2 (0.8 to 1.9)	1.4 (0.8 to 2.5)	0.42	0.18
HbA1c within target without confirmed hypoglycemia, n (%)	9 (39)	5 (23)	4 (15)	3 (12)	2.4 (0.9 to 6.8)	1.9 (0.5 to 7.0)	0.07	0.33

†in accordance with standards of diabetes care, target HbA1c was set ≤ 7.0% (≤ 53 mmol/mol). *p<0.05. Abbreviations: SA = South Asian; WE = Western European.

Table 7. hypoglycemia risk specified by ethnicity

	Liraglutide		Placebo		Mean Δ (95% CI)		*p*-value	
	WE (n=23)	SA (n=22)	WE (n=26)	SA (n=25)	WE	SA	WE	SA
Total hypoglycemic rate, mean/participants (SD)	1.1 (2.1)	2.6 (4.1)	1.5 (2.7)	3.9 (4.1)	-0.4 (-1.8 to 1.0)	-1.3 (-3.7 to 1.1)	0.56	0.27
Total confirmed hypoglycemic rate†, mean/participants (SD)	1.0 (2.0)	2.2 (3.9)	1.4 (2.7)	3.0 (3.7)	-0.4 (-1.8 to 1.0)	-0.9 (-3.1 to 1.4)	0.54	0.44
Severe hypoglycemia, n	0	0	0	0	NA	NA	NA	NA
Grade 2 hypoglycemia, mean/participants (SD)	0.4 (1.1)	0.4 (0.7)	0.1 (0.4)	0.6 (1.1)	0.3 (-0.2 to 0.7)	-0.2 (-0.7 to 0.4	0.25	0.48
Grade 1 hypoglycemia, mean/participants (SD)	0.6 (1.1)	1.8 (3.5)	1.3 (2.5)	2.5 (3.0)	-0.7 (-1.8 to 0.4)	-0.7 (-2.6 to 1.2)	0.22	0.49
Relative hypoglycemia, mean/participants (SD)	0.0 (0.2)	0.1 (0.5)	0.1 (0.3)	0.4 (1.0)	-0.1 (-0.2 to 0.1)	-0.2 (-0.7 to 0.2)	0.13	0.32
Probable hypoglycemia, mean/participants (SD)	0.1 (0.3)	0.2 (0.5)	0.0 (0.0)	0.5 (1.2)	0.1 (-0.0 to 0.2)	-0.3 (-0.8 to 0.3)	0.37	0.38

†Confirmed hypoglycemia was defined as grade 2 or grade 1 hypoglycemia that occurred during the 6-month trial period. Abbreviations: SA = South Asian; WE = Western European.

Discussion

In this heterogenous population of T2DM patients including those using MDI and of SA descent, liraglutide treatment resulted in significantly more participants reaching target HbA1c as compared to placebo added to standard care without increasing hypoglycemia risk. Liraglutide was at least as effective in the subgroup using MDI and did not differ between participants of SA descent as compared to WE participants.

Liraglutide added to MDI regimen

The observation that liraglutide significantly increased the chance of reaching target HbA1c in the subgroup of participants using MDI is the most important finding of this study. In general, patients requiring MDI are difficult to treat with less than 50% reaching HbA1c ≤ 7%[11]. Notwithstanding, the 2018 EASD/ADA T2DM management guideline does not support the initiation of a GLP-1RA when patients fail on MDI regimens[1]. The finding that liraglutide was associated with 41% (9 of 22) of subjects reaching target HbA1c versus 5% (1 of 21) in placebo group could support the consideration of adding liraglutide to an MDI regimen when HbA1c target is not met. Both the glucose-dependent effect of liraglutide as well as its ameliorating effect on glucose variability were probably contributive to these favorable glucoregulatory effects[21]. Incident hypoglycemic events probably avoided further intensification of insulin in the placebo-treated patients.

Our findings are in accordance with previous studies in (morbidly) obese T2DM patients of WE descent using intensive (premix or basal-bolus) insulin therapy (on average > 100 units per day)[14, 15, 22]. Although these studies had a change in HbA1c as the primary outcome, the proportion of patients reaching target Hb1c was reported as an additional outcome parameter. In the study by Lind et al., 43% (27 of 63) reached target HbA1c in the liraglutide arm versus 5% (3 of 59) in placebo-treated patients (mean BMI 34 kg/m^2)[14]. Vanderheiden et al. reported 22% (7 of 32) vs 3% (1 of 34) reaching target HbA1c in liraglutide and placebo arms, respectively (mean BMI 41 kg/m^2)[15]. An open-label randomized study performed in 2014 (mean BMI 41 kg/m^2) reported 43% of participants reaching target HbA1c with addition of liraglutide to

high-dose intensive insulin therapy vs 31% in the control arm using up-titration of insulin[22]. In the FLAT-SUGAR trial (mean BMI 34 kg/m^2), pre-prandial exenatide twice daily did not lower HbA1c but did improve glycemic variability[23].

An important difference between our study population and aforementioned populations is that mean BMI in our MDI subgroup was 30 kg/m^2 (SD 4) with mean insulin dosage of less than 100 IE/day at baseline. In part, this is caused by the fact that 70% of the MDI group consisted of people of SA descent who are characterized by a relatively low BMI. Therefore, our study indicates that liraglutide's efficacy in MDI-treated patients might not be limited to morbidly obese patients of WE descent, but also holds for overweight and mildly obese patients of SA descent.

Liraglutide in South Asians

Further support for this hypothesis is provided by the fact that we did not find a difference in efficacy of liraglutide between SA and WE. Given the relatively low sample size, we can conclude from this that the influence of ethnicity did not transcend the heterogeneity within an ethnic group. This is not surprising given the heterogenous T2DM phenotypes ranging from obese insulin-resistant individuals at one end of the spectrum, to lean insulin-sensitive individuals with primarily beta cell failure on the other end of the spectrum[2, 3]. Some studies focusing on GLP-1RAs and glycemic endpoints have been performed in SA, but have been limited by lack of control arm, which could have caused greater efficacy as compared to the LEAD trials[24]. Randomized trials have been performed in Asia, and when compared to non-Asian dominant studies liraglutide seems more effective: relative risk for achieving the target HbA1c ≤ 7.0% tended to be greater in the Asian-dominant studies [RR 5.7 (3.8, 8.7)] than in the non-Asian-dominant studies [RR 2.8 (2.4, 3.3)][25]. However, SA represented only a minority in these trials. Pathophysiology in SA might be different from West or East Asians: SA have been shown to have higher insulin resistance[5] as well as impaired beta cell function, as compared to other populations[8, 26]. To our knowledge, our study is the first randomized placebo-controlled trial specifically reporting on liraglutide's efficacy and safety on glycemic endpoints in T2DM patients of SA descent.

Clinical impact of the study

Advantageous properties of GLP-1RA therapy are weight loss and low risk of hypoglycemia in patients that are on metformin with or without sulfonylurea derivative with or without basal insulin[1]. Besides providing evidence that liraglutide is effective in patients with T2DM from SA descent, the current study adds to current knowledge that liraglutide is an attractive option for patients that are not in control on MDI regimens. In addition to its favorable glycemic effects, liraglutide has been shown to reduce body weight and major cardiovascular adverse events[13], possibly related to a direct cardioprotective mechanism[27]. In that regard, the indication of GLP-1RA therapy must be viewed in the context of prevention of major cardiovascular events. For the purpose of glycemic control, the addition of a GLP-1RA to an MDI regimen must be viewed in the context of other available strategies, such as intensive lifestyle intervention[28], bariatric surgery[29], addition of SGLT2-inhibitors[30] or continuous subcutaneous insulin pump therapy[31]. Comparative studies with these interventions are currently lacking.

Limitations

The results of this secondary study should be interpreted with caution, especially with regard to the number of participants using MDI (45% of study population, n = 43). The sample size may have been too small for the reported endpoints, which could have increased the likelihood of type 1 errors. Furthermore, with the sample size of 96 patients, more subtle differences between liraglutide efficacy between SA and WE cannot be detected. Although participants were explicitly asked about hypoglycemic events on a weekly basis, and ambulant blood glucose values were collected at the end of the studies, we cannot fully exclude under-reporting of hypoglycemic episodes. Importantly, the double-blind study design has precluded a skewed under-reporting between study groups. Another limitation of this study is that we did not assess euglycemic clamps and systematic evaluation of residual beta cell function. Hence, mechanisms underlying success or failure of liraglutide could not be further studied.

Conclusion

To conclude, this study shows that addition of liraglutide in Dutch WE and Dutch SA people with T2DM using metformin, sulfonylurea derivative and/or insulin increases the chance of reaching target HbA1c without increasing the risk of hypoglycemia. In patients already using an MDI regimen, liraglutide significantly improved the chance of achieving adequate glycemic control. There was no difference between WE and SA in terms of liraglutide efficacy. This study therefore suggests that addition of liraglutide should be considered, especially when up-titration of insulin with an MDI regimen is hampered by hypoglycemic episodes. Future studies should focus on determinants of liraglutide efficacy such as relative beta cell function and insulin resistance.

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