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Original Article

Comparison of Efficacy and Safety of Liraglutide 3.0 mg in Individuals with BMI above and below 35 kg/m^2: A Post-hoc Analysis

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Liraglutide · Obesity · Efficacy · Safety

Abstract
Objective: To investigate whether the efficacy and safety of liraglutide 3.0 mg differed between two subgroups, BMI 27 to <35 and BMI ≥ 35 kg/m^2, in individuals without and with type 2 diabetes (T2D). ***Methods:*** A post-hoc analysis of two 56-week, randomized, double-blind, placebo-controlled trials (SCALE Obesity and Prediabetes; SCALE Diabetes). Subgroup differences in treatment effects of liraglutide 3.0 mg were evaluated by testing the interaction between treatment group and baseline BMI subgroup. ***Results:*** Significantly greater weight loss (0–56 weeks) was observed with liraglutide 3.0 mg versus placebo in all patient groups while on treatment. There was no evidence that the weight-lowering effect of liraglutide 3.0 mg differed between BMI subgroups (interaction $p > 0.05$). Similarly, for most secondary endpoints significantly greater improvements were observed with liraglutide 3.0 mg versus placebo, with no indication treatment effects differing between subgroups. The safety profile of liraglutide 3.0 mg was broadly similar across BMI subgroups. ***Conclusion:*** This post-hoc analysis did not indicate any differences in the treatment effects, or safety profile, of liraglutide 3.0 mg for individuals with BMI 27 to <35 or ≥35 kg/m^2. Liraglutide 3.0 mg can therefore be considered for individuals with a BMI of ≥35 as well as for those with a BMI of 27 to <35 kg/m^2.

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Introduction

Obesity (BMI ≥ 30 kg/m^2) is a global health issue, the prevalence of which has risen over the last three decades [1]. This increasing prevalence is of clinical concern as the risk of death is increased in individuals who have overweight/obesity [2, 3].

The increasing prevalence of the higher obesity classes (class II (BMI ≥ 35 to 40 kg/m^2), III (BMI ≥ 40 to 50 kg/m^2), IV (BMI ≥ 50 to 60 kg/m^2), V (≥60 kg/m^2)), and the associated risk of complications associated with these BMI classes are of clinical importance. In the US, the prevalence of higher obesity classes increased at the fastest rates between 2001 and 2010, with prevalence of class III obesity rising by 70% and classes IV and above by >70% [4].

Meta-analyses of prospective studies indicate that individuals with a BMI of 35–40 kg/m^2 have higher rates of all-cause mortality than those with a BMI in the healthy range (n = 1.46 million, hazard ratio 1.88 (95% confidence interval (CI) 1.77–2.00) [2]; n = 3,950,000, hazard ratio 1.94 (95% CI 1.87–2.01) [3]). The prevalence of type 2 diabetes (T2D), gallbladder disease, coronary heart disease, and high blood pressure are all increased in people with overweight and obesity classes I, II and III, compared with subjects of normal weight [5]. Furthermore, a BMI above the healthy range (18.5 to ≤25 kg/m^2) translates into increased cost burdens, and it has been estimated that healthcare costs for the treatment of obesity-related diseases and medicine costs increase by 4% and 7%, respectively, for every unit of BMI above normal [6].

There are many weight management strategies, and current options include dietary therapy, physical activity, behavioral therapy, pharmacotherapy, and bariatric surgery (or combinations thereof). Intervention for individuals with a BMI ≥27 kg/m^2 with a concurrent comorbidity (including diabetes) and intensification of treatment in higher obesity classes, have been suggested [7]. Many professional bodies, e.g. the American Diabetes Association (ADA) [8], the Canadian Medical Association (CMA) [9], the European Association for the Study of Obesity (EASO) [10], the American Heart Association (AHA)/American College of Cardiology (ACC)/The Obesity Society (TOS) [7], and the UK National Institute for Health and Clinical Excellence (NICE) [11], specify consideration of bariatric surgery for individuals with BMI > 35 kg/m^2 plus a weight-related comorbidity.

Interventions vary in effectiveness, but, encouragingly, even modest (5–10%) weight loss is associated with clinically meaningful health benefits [12]. Lifestyle interventions can achieve weight loss of 4–7%, whereas a 15–50% reduction in body weight can occur with surgery (depending on procedure). A treatment gap exists, however, for individuals with overweight/obesity who do not respond sufficiently to lifestyle interventions and are unable to, or do not wish to, undergo bariatric surgery.

Liraglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for weight management (at a dose of 3.0 mg) in individuals with BMI ≥ 27 kg/m^2 plus at least one weight-related comorbidity or in those with obesity (BMI ≥ 30 kg/m^2) [13] has achieved clinically relevant weight loss in individuals with overweight/obesity, both without and with T2D [14, 15].

Given the limited choice of effective interventions available for the treatment of adults with overweight/obesity, a post-hoc analysis of two phase IIIa studies was performed to establish whether the weight-lowering efficacy of liraglutide persists in higher BMI subgroups. In this analysis, the efficacy and safety of liraglutide 3.0 mg were compared in individuals with a BMI 27 to <35 and ≥35 kg/m^2 (the BMI where surgery is considered in many national guidelines) in populations without and with T2D.

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Material and Methods

Clinical Trials

Two clinical trials were included in this post-hoc analysis; both were phase III, 56-week, randomized, double-blind, placebo-controlled, multicenter trials that recruited adults (≥18 years) with either obesity (BMI ≥ 30.0 kg/m^2) or overweight (BMI ≥ 27.0 kg/m^2) plus at least one weight-related comorbidity. These trials were chosen from the Satiety and Clinical Adiposity: Liraglutide Evidence (SCALE) program [14–17] because they were both of 1 year's duration and were similar in design. The trials have been described in full elsewhere, but key information is summarized below [14, 15]:

(1) In both trials:
- All individuals were advised by a qualified dietician throughout the trial, in group or individual counselling sessions, on a 500 kcal/day-deficit diet and instructed to exercise ≥150 min/week, and re-enforced through use of pedometers.
- Liraglutide dose escalation (0.6 mg weekly increments) occurred during weeks 0–4.
- Body weight was recorded to the nearest 0.1 kg and measured in a fasting state (≥8-hour overnight fast without food and/or drink intake, except for water).
- All individuals had previously failed dietary effort and stable body weight (<5 kg self-reported change) for the 3 months before entering the studies.

(2) In SCALE Obesity and Prediabetes (clinical trial in individuals without T2D):
- Individuals were recruited with normoglycemia or pre-diabetes (ADA 2010 criteria) [18] and either a BMI of ≥30 kg/m^2, or of ≥27 kg/m^2 if they also had concomitant treated or untreated dyslipidemia and/or hypertension.
- At screening individuals were randomized 2:1 to once-daily liraglutide or placebo, and stratified according to prediabetes status (yes; no) and BMI (≥30; <30 kg/m^2).
- Exclusion criteria included: HbA_{1c} ≥ 6.5%, fasting plasma glucose (FPG) ≥ 7.0 mmol/l, or 2-hour post-challenge plasma glucose ≥ 11.1 mmol/l.

(3) In SCALE Diabetes (clinical trial in individuals with T2D):
- Individuals were recruited with T2D (HbA_{1c} 7.0–10.0%) and a BMI of ≥27 kg/m^2. Inclusion criteria included treatment for T2D with either diet/exercise alone or any of the following (single agent or in combination): metformin, sulfonylurea, and/or glitazone. Pre-trial, sulfonylurea dose was reduced by 50% to mitigate potential hypoglycemia.
- At screening, individuals were randomized 2:1:1 to once daily liraglutide 3.0 mg, 1.8 mg, or placebo, given as add-on to background T2D treatment, and stratified according to background T2D treatment and by HbA_{1c} (<8.5%; ≥8.5%).
- Exclusion criteria included: use of any of GLP-1 RA, dipeptidyl peptidase-4 inhibitor (DPP-4i), or insulin within the last 3 months, uncontrolled hypertension (systolic blood pressure (SBP) ≥160 mm Hg and/or diastolic blood pressure (DBP) ≥100 mm Hg).

Data Analysis

The treatment effects of liraglutide across baseline BMI subgroups (27 to <35 vs. ≥35 kg/m^2) were evaluated by statistical testing of interaction between treatment group (liraglutide 3.0 mg; placebo) and baseline BMI subgroup. Efficacy endpoints were analyzed using data from the full analysis set (FAS; all randomized, exposed individuals, with at least one post-baseline assessment of any efficacy endpoint). Safety outcomes were described using data from the safety analysis set (SAS; all randomized, exposed individuals).

Continuous efficacy variables (change from baseline to week 56) were analyzed using an analysis of covariance (ANCOVA) model. Baseline values were included as covariates in the model, with treatment, baseline BMI subgroup, interaction between treatment and baseline BMI subgroup, country, and sex as fixed factors. For SCALE Obesity and Prediabetes, additional fixed factors included baseline prediabetes status, BMI strata at baseline, and interaction between baseline prediabetes status and BMI strata. For SCALE Diabetes, additional fixed factors were background T2D treatment, HbA_{1c} strata, and interaction between background T2D treatment and HbA_{1c} strata.

Achievement of categorical weight loss at week 56 (≥5%, >10% and >15% weight loss, when compared with baseline body weight) was analyzed using a logistic regression model. The same fixed factors as the ANCOVA model were used, with baseline fasting body weight as covariate.

For SCALE Diabetes, only liraglutide 3.0 mg and placebo data were included in the analyses; liraglutide 1.8 mg data were excluded (liraglutide 3.0 mg is the only approved dose for weight management).

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Table 1. Baseline demographics and characteristics for individuals without and with diabetes, by baseline BMI 27 to <35 and ≥ 35 kg/m^2*

	Individuals without diabetes, n = 3,662			
	baseline BMI 27 to <35 kg/m^2, n = 1,279		baseline BMI ≥ 35 kg/m^2, n = 2,383	
	liraglutide 3.0 mg, n = 856	placebo, n = 423	liraglutide 3.0 mg, n = 1,581	placebo, n = 802
Body weight, kg	90.1 (11.0)	89.9 (11.1)	115.1 (20.2)	115.0 (20.9)
BMI, kg/m^2	32.4 (1.6)	32.3 (1.8)	41.5 (5.7)	41.5 (5.5)
Female, %	76.9	78.7	79.4	77.7
Age, years	46.8 (12.2)	46.3 (11.5)	44.3 (11.9)	44.3 (12.2)
Prediabetes, %	54.0	51.1	65.3	66.1
HbA_{1c}, %	5.5 (0.4)	5.5 (0.4)	5.6 (0.4)	5.6 (0.4)
FPG, mmol/l	5.3 (0.6)	5.2 (0.5)	5.3 (0.6)	5.3 (0.5)
SBP, mm Hg	121.4 (13.0)	120.9 (13.0)	123.9 (12.8)	124.5 (12.5)
DBP, mm Hg	77.6 (8.6)	77.4 (8.7)	79.2 (8.6)	79.6 (8.3)
	Individuals with diabetes, n = 623			
	baseline BMI 27 to <35 kg/m^2, n=273		baseline BMI ≥ 35 kg/m^2, n=350	
	liraglutide 3.0 mg, n = 185	placebo, n = 88	liraglutide 3.0 mg, n = 227	placebo, n = 123
Body weight, kg	91.4 (12.2)	91.4 (12.7)	117.2 (21.2)	117.5 (19.3)
BMI, kg/m^2	31.5 (2.1)	31.4 (2.2)	41.7 (5.2)	41.6 (6.3)
Female, %	40.0	47.7	54.2	58.5
Age, years	57.6 (9.3)	56.4 (10.2)	52.9 (11.2)	53.6 (9.5)
Prediabetes, %	n/a	n/a	n/a	n/a
HbA_{1c}, %	7.9 (0.8)	7.9 (0.8)	8.0 (0.8)	7.9 (0.8)
FPG, mmol/l	8.8 (2.0)	8.5 (1.8)	8.8 (1.7)	8.7 (1.8)
SBP, mm Hg	128.4 (13.0)	129.2 (13.7)	129.3 (14.1)	129.2 (13.5)
DBP, mm Hg	78.1 (9.1)	77.8 (9.3)	79.7 (8.1)	80.3 (9.5)

*Data are based on the full analysis set and presented as observed means (SD), or observed proportions.

DBP = Diastolic blood pressure; FPG = fasting plasma glucose; HbA_{1c} = glycocylated hemoglobin; SBP = systolic blood pressure; SD = standard deviation of the mean.

For endpoints measured as continuous variables, missing data were imputed using the last observation carried forward (LOCF) method. For achievement of categorical weight loss (≥5%, >10%, and >15%), missing data were imputed using LOCF before dichotomization. Baseline demographic and safety outcomes are based on observed means/proportions. Unless otherwise stated, efficacy endpoints are presented as estimated means or proportions adjusted to the observed baseline distribution of the individuals included in the models for each BMI subgroup.

Uncommon events (e.g. pancreatitis and other hepatobiliary events) were not statistically analyzed due to the low number of events in both treatment groups. For pancreatitis, only event committee-adjudicated events are shown (safety data for all events, including non-adjudicated events, have been reported elsewhere [14, 15]). Event adjudication was performed by an independent external committee of medical experts and was a blinded process.

Results

Baseline Demographics

In general, baseline demographics were similar across treatment arms and BMI subgroups (table 1). In SCALE Obesity and Prediabetes, more individuals with BMI ≥ 35 than 27 to <35

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kg/m^2 were classified as having prediabetes at screening (table 1). In SCALE Diabetes, there was a slightly higher proportion of female individuals with a BMI ≥35 than with 27 to <35 kg/m^2 (individuals with T2D, table 1).

Efficacy (Body Weight) Endpoints

Significantly greater weight loss was seen from baseline to 56 weeks on treatment with liraglutide 3.0 mg when compared with placebo in individuals without and with T2D (fig. 1a,b). Analysis of the interaction between treatment effect and baseline BMI subgroup (27 to <35 and ≥35 kg/m^2) revealed no evidence that the effect of liraglutide 3.0 mg on body weight differed between the two baseline BMI subgroups (interaction $p > 0.05$; fig, 1a, 2).

Similarly, statistically significantly more individuals (without and with T2D) achieved ≥5%, 10%, and 15% categorical weight loss at week 56 with liraglutide 3.0 mg, than with placebo (fig. 2), with no evidence to suggest that the effect of liraglutide 3.0 mg on categorical weight loss achievement differed between the two baseline BMI subgroups (interaction $p > 0.05$). Estimated treatment differences between the treatment arms (liraglutide 3.0 mg vs. placebo) for continuous efficacy endpoints, and odds ratios (liraglutide 3.0 mg vs. placebo) for the achievement of categorical efficacy endpoints are stated in table 3, with corresponding 95% CIs.

Efficacy (Non-Body Weight) Endpoints

For the majority of secondary endpoints, statistically significantly greater improvements were seen with liraglutide 3.0 mg versus placebo from baseline to 56 weeks in individuals without and with T2D (waist circumference (fig.1c), HbA_{1c} (fig. 1d), fasting plasma glucose (fig. 1e), and blood pressure (fig. 1f)). Furthermore, for the majority of secondary endpoints, analysis of the interaction between treatment group and BMI subgroup revealed no evidence that the effects of liraglutide 3.0 mg differed between the BMI subgroups (interaction $p > 0.05$, fig. 1c–g). However, for individuals without T2D, greater improvement relative to placebo in the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire score related to physical function was recorded for individuals with baseline BMI ≥ 35 kg/m^2 (interaction p value = 0.04; fig. 1g). The same trend was seen in individuals with T2D, with greater mean improvement in IWQOL-Lite physical function score under liraglutide 3.0 mg treatment compared with placebo occurring in the high BMI subgroup. However, this difference between BMI subgroups was not statistically significant (interaction $p = 0.05$; fig. 1g).

Statistically significantly greater reductions in HbA_{1c} and FPG were seen with liraglutide 3.0 mg than with placebo in individuals without and with T2D, with no evidence that the effect of liraglutide 3.0 mg treatment on glycemic reduction differed between the two baseline BMI subgroups (interaction $p > 0.05$; fig. 1d,e). Similarly, there was no evidence that the effect of liraglutide 3.0 mg treatment on blood pressure reduction differed between the two baseline BMI subgroups (interaction $p > 0.05$; fig. 1f).

Safety Outcomes

Overall, treatment-emergent adverse events (AEs) and treatment-emergent serious AEs were broadly similar across the BMI subgroups (table 2). Rates of gallbladder disorders were low, but numerically higher with liraglutide 3.0 mg than with placebo, and the frequency of these outcomes was similar across BMI subgroups (table 2). No individuals with T2D experienced acute pancreatitis in either treatment group. The number of individuals without T2D experiencing adjudicated acute pancreatitis events was low, but numerically higher with liraglutide 3.0 mg than with placebo; the frequency of acute pancreatitis events in these individuals was similar across BMI subgroups (table 2). The most frequently reported AEs were gastrointestinal (GI); rates of GI disorders were broadly similar across BMI subgroups, but higher with liraglutide 3.0 mg than with placebo (table 2).

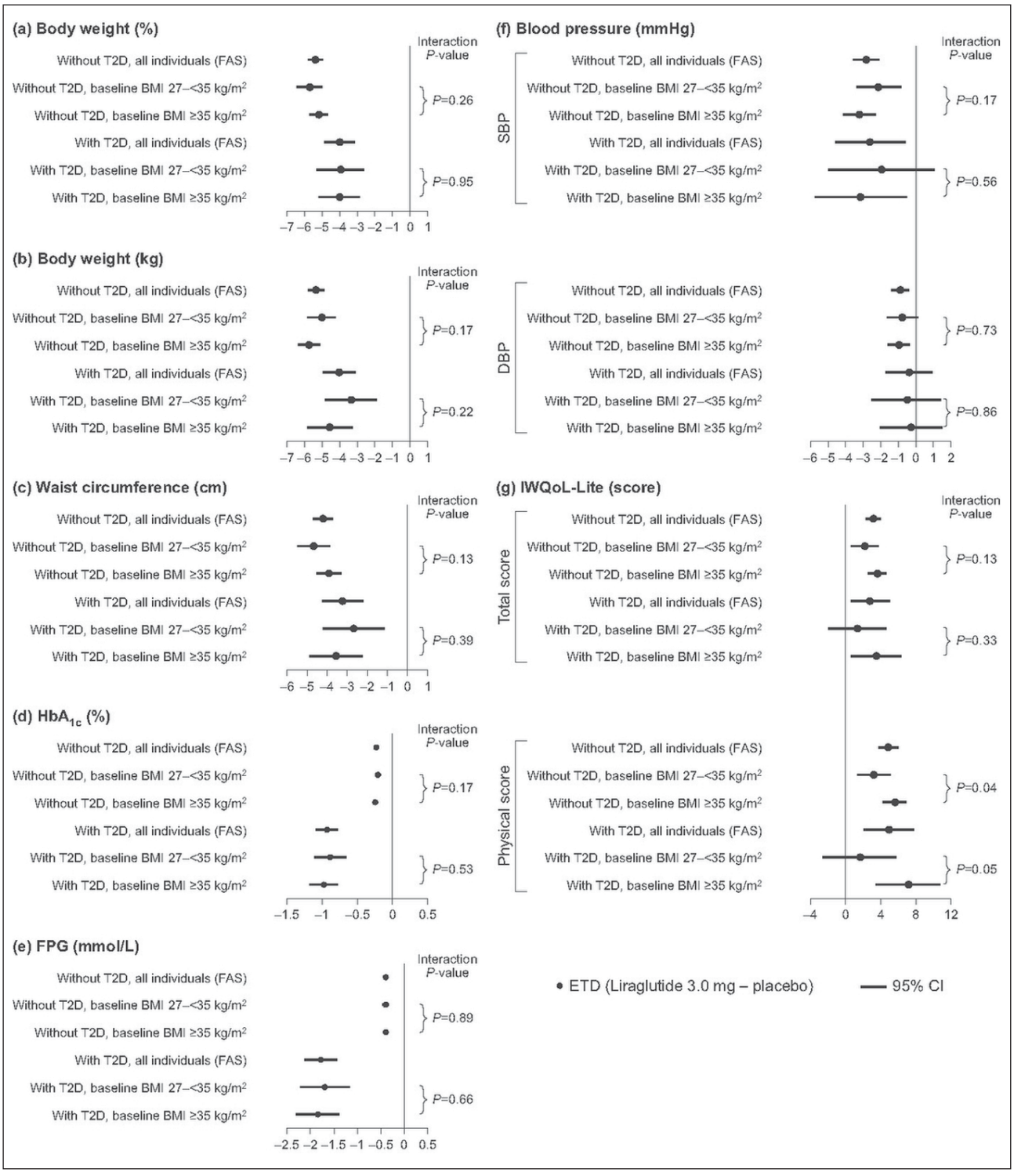

Fig. 1. Forest plots showing the treatment effects of liraglutide 3.0 mg, by baseline BMI 27 to <35 and ≥35 kg/m². Data are 0–56 weeks for the full analysis set. Statistical analysis is analysis of covariance with last observation carried forward. P-values are based on a test of interaction between treatment effect and baseline BMI subgroup and reflect the evidence of a difference in treatment effect between BMI subgroups. ETDs refer to change from baseline to 56 weeks (liraglutide 3.0 mg – placebo). CI = Confidence interval; DBP = diastolic blood pressure; ETD = estimated treatment difference; FAS = full analysis set; FPG = fasting plasma glucose; HbA_{1c} = glycated hemoglobin; IWQOL-Lite = Impact of Weight of Quality of Life-Lite questionnaire; SBP = systolic blood pressure; T2D = type 2 diabetes.

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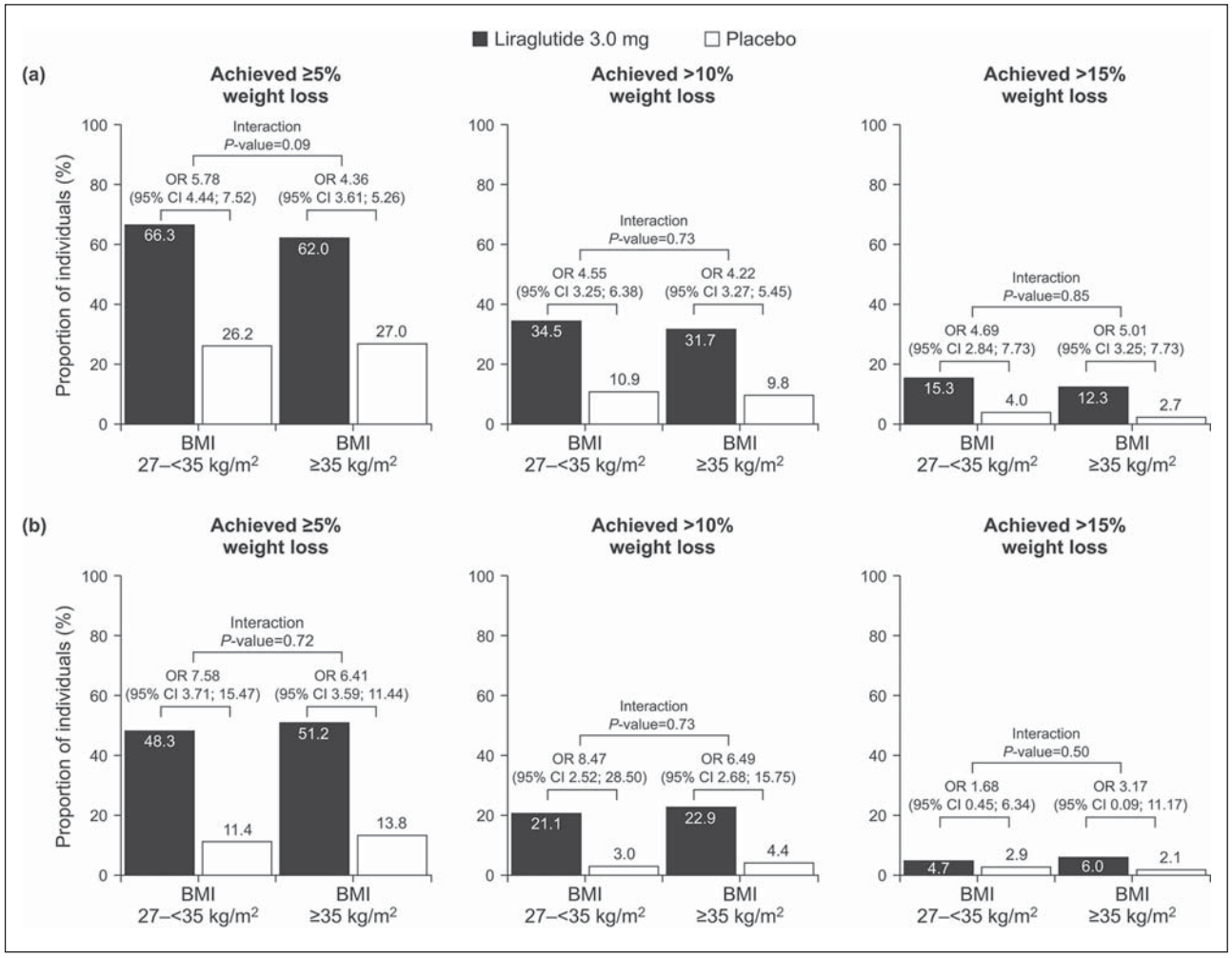

Fig. 2. Achievement of categorical fasting weight-loss (loss of ≥5%, >10%, and >15% body weight at 56 weeks) by baseline BMI and diabetes status. Statistical analysis is analysis of covariance with last observation carried forward. Data are model-based estimates of ORs and proportions, based on the full analysis set. Estimated proportions are adjusted to the observed baseline distribution of the individuals included in the models in each BMI subgroup. Interaction p values are based on a test of interaction between treatment effect and baseline BMI subgroup and reflect the evidence for a difference in treatment effect between BMI subgroups. CI = Confidence interval; OR = odds ratio.

The change in pulse observed with liraglutide 3.0 mg was similar across BMI subgroups. For individuals without T2D the mean pulse rate increased by 3.1 beats/min (bpm) (<35 kg/m^2) and 2.3 bpm (≥35 kg/m^2), with similar increases observed in individuals with T2D (2.3 and 1.7 bpm, respectively) (table 2). A 2–3 bpm increase in heart rate associated with liraglutide 3.0 mg has been described previously [14, 15]; however, the clinical significance of increases in heart rate occurring with GLP-1 receptor agonists is unknown [19].

Overall withdrawal rates were lower with liraglutide 3.0 mg than with placebo in individuals without (n = 698/2,487 (28.1%) vs. n = 443/1,244 (35.6%)) and with T2D (n = 99/423 (23.4%) vs. n = 72/212 (34.0%)). More individuals withdrew from the trial due to AEs with liraglutide. For individuals with T2D, rates of withdrawals due to AEs were numerically higher in the low BMI than in the high BMI subgroup in both treatment arms (table 2).

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Table 2. Safety outcomes in individuals without and with diabetes*, by baseline BMI 27 to <35 and ≥ 35 kg/m$^{2\#}$

	Individuals without diabetes, n = 3,723							
	baseline BMI 27 to <35 kg/m^2, n = 1,304				baseline BMI ≥ 35 kg/m^2, n = 2,419			
	liraglutide 3.0 mg, n = 873		placebo, n = 431		liraglutide 3.0 mg, n = 1,608		placebo, n = 811	
	n (%)	E (R)	n (%)	E (R)	n (%)	E (R)	n (%)	E (R)
Overall adverse events	798 (91.4)	4,791 (606.9)	368 (85.4)	1,875 (499.8)	1,487 (92.5)	9,239 (639.3)	675 (83.2)	3,354 (484.5)
Serious adverse events	52 (6.0)	62 (7.9)	25 (5.8)	32 (8.5)	102 (6.3)	132 (9.1)	37 (4.6)	43 (6.2)
Severe adverse events	92 (10.5)	137 (17.4)	41 (9.5)	51 (13.6)	212 (13.2)	311 (21.5)	72 (8.9)	112 (16.2)
Adverse events leading to withdrawal	94 (10.8)	143 (18.1)	20 (4.6)	26 (6.9)	153 (9.5)	231 (16.0)	29 (3.6)	47 (6.8)
Gastrointestinal adverse events	598 (68.5)	1,707 (216.2)	192 (44.5)	387 (103.2)	1,097 (68.2)	3,342 (231.2)	309 (38.1)	610 (88.1)
Nausea	350 (40.1)	489 (61.9)	63 (14.6)	75 (20.0)	647 (40.2)	940 (65.0)	120 (14.8)	148 (21.4)
Vomiting	137 (15.7)	208 (26.3)	17 (3.9)	19 (5.1)	267 (16.6)	389 (26.9)	34 (4.2)	43 (6.2)
Gallbladder disorders	18 (2.1)	19 (2.4)	3 (0.7)	4 (1.1)	37 (2.3)	42 (2.9)	7 (0.9)	8 (1.2)
Change in pulse, beats/min (SD)	+3.1 (9.5)		+0.1 (8.9)		+2.3 (10.0)		+0.1 (9.9)	
Acute pancreatitis	2 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	3 (0.2)	3 (0.2)	0 (0.0)	0 (0.0)
	Individuals with diabetes, n = 634							
	baseline BMI 27 to <35 kg/m^2, n = 280				baseline BMI ≥ 35 kg/m^2, n = 354			
	liraglutide 3.0 mg, n = 191		placebo, n = 89		liraglutide 3.0 mg, n = 231		placebo, n=123	
	n (%)	E (R)	n (%)	E (R)	n (%)	E (R)	n (%)	E (R)
Overall adverse events	179 (93.7)	1,655 (966)	74 (83.1)	424 (574)	213 (92.2)	2,070 (992)	108 (87.8)	615 (581)
Serious adverse events	18 (9.4)	22 (13)	5 (5.6)	9 (12)	19 (8.2)	28 (13)	8 (6.5)	11 (10)
Severe adverse events	26 (13.6)	35 (20)	11 (12.4)	17 (23)	26 (11.3)	48 (23)	10 (8.1)	13 (12)
Adverse events leading to withdrawal	25 (13.1)	32 (19)	4 (4.5)	4 (5)	14 (6.1)	19 (9)	3 (2.4)	3 (3)
Gastrointestinal adverse events	128 (67.0)	353 (206.1)	28 (31.5)	65 (88.1)	147 (63.6)	498 (238.8)	55 (44.7)	85 (80.3)
Nausea	64 (33.5)	93 (54.3)	11 (12.4)	13 (17.6)	74 (32.0)	115 (55.1)	18 (14.6)	21 (19.8)
Vomiting	20 (10.5)	31 (18.1)	7 (7.9)	7 (9.5)	46 (19.9)	82 (39.3)	5 (4.1)	7 (6.6)
Documented symptomatic hypoglycemic events†	45 (23.6)	184 (107)	11 (12.4)	24 (33)	52 (22.5)	145 (70)	16 (13.0)	32 (30)
Gallbladder disorders	2 (1.0)	2 (1.2)	1 (1.1)	1 (1.4)	2 (0.9)	3 (1.4)	0 (0.0)	0 (0.0)
Change in pulse, beats/min (SD)	+2.3 (9.0)		−0.3 (8.8)		+1.7 (10.3)		−2.2 (9.6)	
Acute pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

#Safety analysis set. Data are presented as n (%), except pulse which is observed mean change from baseline (SD), with LOCF. % are based on total of BMI-subgroup treatment arm. Pancreatitis data are Event Adjudication Committee-confirmed events.

*Treatment emergent adverse events occurring in weeks 0–56 (SCALE Obesity and Prediabetes), or weeks 0–58 (SCALE Diabetes (includes a 2-week off-drug follow up period)).

†According to American Diabetes Association 2010 criteria.

n = Number of individuals; E = number of events; LOCF = last observation carried forward; PYE = patient-years of exposure; R = event rate per 100 years of patient exposure; SD = standard deviation of the mean.

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Table 3. Treatment effects of liraglutide for efficacy endpoints in individuals without and with diabetes, by baseline BMI 27 to <35 and ≥ 35 kg/m^2*

	Individuals without diabetes, n = 3,662						
	baseline BMI 27 to <35 kg/m^2, n = 1,279 change from baseline to 56 weeks			baseline BMI ≥ 35 kg/m^2, n = 2,383 change from baseline to 56 weeks			interaction p value
	liraglutide 3.0 mg, n = 856	placebo, n = 423	ETD (95% CI)	liraglutide 3.0 mg, n = 1,581	placebo, n = 802	ETD (95% CI)	
Body weight, %	–8.2	–2.7	–5.73 (–6.47; –4.99)	–7.9	–2.6	–5.20 (–5.74; –4.66)	0.26
Body weight, kg	–7.3	–2.4	–5.10 (–5.91; –4.29)	–8.9	–3.1	–5.81 (–6.40; –5.22)	0.17
Waist circumference, cm	–8.2	–3.5	–4.68 (–5.49; –3.87)	–8.2	–4.2	–3.90 (–4.49; –3.31)	0.13
HbA_{1c}, %	–0.3	–0.1	–0.21 (–0.24; –0.18)	–0.3	–0.1	–0.24 (–0.26; –.021)	0.17
FPG, mmol/l	–0.4	0.0	–0.38 (–0.44; –0.32)	–0.4	0.0	–0.38 (–0.43; –0.34)	0.89
SBP, mm Hg	–3.7	–1.4	–2.11 (–3.36; –0.87)	–4.5	–1.6	–3.19 (–4.09; –2.28)	0.17
DBP, mm Hg	–2.5	–1.8	–0.75 (–1.64; 0.14)	–2.7	–1.9	–0.95 (–1.60; –0.30)	0.73
IWQOL-Lite total score (arbitrary units)#	9.1	7.1	2.16 (0.65; 3.67)	11.4	8.0	3.59 (2.51; 4.67)	0.13
IWQOL-Lite physical score (arbitrary units)	10.0	7.4	3.19 (1.33; 5.05)	15.0	9.3	5.59 (4.26; 6.92)	0.04
	Individuals with diabetes, n = 632						
	baseline BMI 27 to <35 kg/m^2, n = 273 change from baseline to 56 weeks			baseline BMI ≥ 35 kg/m^2, n = 350 change from baseline to 56 weeks			interaction p value
	liraglutide 3.0 mg, n = 185	placebo, n = 88	ETD (95% CI)	liraglutide 3.0 mg, n = 227	placebo, n = 123	ETD (95% CI)	
Body weight, %	–5.7	–1.8	–3.95 (–5.27; –2.63)	–6.1	–2.1	–4.01 (–5.15; –2.86)	0.95
Body weight, kg	–5.1	–1.7	–3.43 (–4.87; –1.99)	–7.1	–2.5	–4.63 (–5.88; –3.38)	0.22
Waist circumference, cm	–5.4	–2.7	–2.66 (–4.17; –1.16)	–6.6	–2.8	–3.54 (–4.84 ; –2.24)	0.39
HbA_{1c}, %	–1.2	–0.4	–0.88 (–1.10; –0.66)	–1.4	–0.3	–0.97 (–1.17; –0.78)	0.53
FPG, mmol/l	–1.9	–0.1	–1.68 (–2.20; –1.15)	–1.9	0.0	–1.83 (–2.29; –1.37)	0.66
SBP, mm Hg	–1.9	–0.4	–1.92 (–4.94; 1.09)	–3.6	–0.4	–3.11 (–5.73; –0.50)	0.56
DBP, mm Hg	–0.9	–0.1	–0.49 (–2.52; 1.53)	–0.9	–0.9	–0.25 (–2.00; 1.51)	0.86
IWQOL-Lite total score (arbitrary units)#	9.1	7.2	1.34 (–1.95; 4.62)	14.0	8.0	3.49 (0.62; 6.36)	0.33
IWQOL-Lite physical score (arbitrary units)	12.1	9.4	1.57 (–2.62; 5.77)	18.0	8.5	7.09 (3.43; 10.74)	0.05

*Data are based on the full analysis set. Means are estimated mean change from baseline to 56 weeks, adjusted to the observed baseline distribution of the individuals included in the models in each BMI subgroup. Interaction p values reflect evidence of a difference in treatment effect between BMI subgroups. ETDs are liraglutide 3.0 mg – placebo.

#A higher IWQOL-Lite questionnaire score indicates a better quality of life.

CI = confidence interval; DBP = diastolic blood pressure; ETD = estimated treatment difference; FPG = fasting plasma glucose; IWQOL-Lite = Impact of Weight on Quality of Life-Lite questionnaire; SBP = systolic blood pressure.

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In individuals with T2D, rates of documented symptomatic hypoglycemia were low, but higher with liraglutide 3.0 mg than with placebo in both BMI subgroups (table 2). In the liraglutide 3.0 mg treatment arm of SCALE Diabetes, two individuals with baseline BMI 27 to <35 kg/m^2, and one with BMI ≥ 35 kg/m^2, experienced severe hypoglycemia, whereas no events were observed under placebo treatment.

Discussion

In individuals both without and with T2D, liraglutide 3.0 mg was effective and well tolerated, irrespective of BMI subgroup. There was no evidence that the weight-lowering effect of liraglutide 3.0 mg differed between BMI subgroups (fig. 1a,b, 2; tables 3, 4).

All individuals received a lifestyle (i.e. diet and exercise) intervention that included dietary advice from a qualified dietician, in line with AHA/ACC/TOS guidelines [7]. It has been reported that dietician-delivered counselling is more effective than physician-delivered outpatient programs, achieving ~3–6 kg weight loss in individuals with overweight/obesity [20]. Weight loss was expected with placebo as a result of the robust diet and exercise intervention, so it was encouraging the estimated treatment difference between liraglutide and placebo indicated that the additional weight loss achieved with liraglutide was clinically relevant for individuals both without (–5.4% (fig. 1a, all individuals)) and with T2D (–4.0% (fig. 1a, all individuals)).

The magnitude of the body weight reductions achieved while on treatment with liraglutide 3.0 mg ranged between an estimated mean weight loss of 5.7% (BMI 27 to <35 kg/m^2 with T2D) and 8.2% (BMI 27 to 35 kg/m^2 without T2D) in the BMI subgroups analyzed (table 3). These reductions are likely to be clinically beneficial given compelling evidence that 5–10% weight loss is associated with improved glucose and lipid metabolism, lower incidence of T2D, improved psychosocial outcomes, and reductions in several other weight-related comorbidities (hypertension, sleep apnea, osteoarthritis) [12, 21–25].

The high BMI subgroup had greater absolute (kg) weight loss compared with the low BMI subgroup (fig. 1b), but had a smaller proportional weight loss (% change from baseline) than the low BMI subgroup (fig. 1a). This discrepancy reflects that in the high BMI subgroup, each additional kg of body weight loss corresponds to a smaller %-change than in the low BMI subgroup.

Previously published phase III data indicate that liraglutide 3.0 mg has a range of beneficial secondary effects, including improvements in glycemic endpoints, blood pressure and overall health-related quality of life in individuals without [14] and with [15] T2D. In the current analysis, for most endpoints there was no evidence to suggest that the effects of liraglutide 3.0 mg differed between BMI subgroups in individuals with or without T2D. The IWQOL-Lite Questionnaire Physical Function score improved more with liraglutide compared with placebo in the high BMI subgroups; however it is beyond the scope of this study to investigate this aspect further.

The overall safety profile of liraglutide 3.0 mg was broadly similar for both BMI subgroups. As reported elsewhere, the most common AEs associated with liraglutide were GI-related [14, 15]. GI side effects are common with the GLP-1RA drug class, mainly occurring transiently during dose escalation [26]. There is evidence for an exposure-–response relationship between liraglutide and GI AEs (and a tendency for lower drug exposure in heavier individuals) [27]. However, rates of GI AEs were similar in both BMI subgroups. Similarly, rates of AEs of special interest (gallbladder disorders, adjudicated acute pancreatitis) were comparable across the BMI subgroups analyzed.

Table 4. Achievement of categorical fasting weight loss (liraglutide 3.0 mg/placebo), by baseline BMI 27 to 35 and ≥ 35 kg/m^2*

	Individuals without diabetes, n = 3,662						
	baseline BMI 27 to <35 kg/m^2, n = 1,279 proportion achieved categorical weight loss after 56 weeks (%)			baseline BMI ≥ 35 kg/m^2, n = 2,383 proportion achieved categorical weight loss after 56 weeks (%)			interaction p value
	liraglutide 3.0 mg, n = 856	placebo, n = 423	OR (95% CI)	liraglutide 3.0 mg, n = 1,581	placebo n = 802	OR (95% CI)	
≥5% weight loss, %	66.3	26.2	5.78 (4.44; 7.52)	62.0	27.0	4.36 (3.61; 5.26)	0.09
>10% weight loss, %	34.5	10.9	4.55 (3.25; 6.38)	31.7	9.8	4.22 (3.27; 5.45)	0.73
>15% weight loss, %	15.3	4.0	4.69 (2.84; 7.73)	12.3	2.7	5.01 (3.25; 7.73)	0.85
	Individuals with diabetes, n = 632						
	baseline BMI 27 to <35 kg/m^2, n = 273 proportion achieved categorical weight loss after 56 weeks (%)			baseline BMI ≥ 35 kg/m^2, n = 350 proportion achieved categorical weight loss after 56 weeks (%)			interaction p value
	liraglutide 3.0 mg, n = 185	placebo, n = 88	OR (95% CI)	liraglutide 3.0 mg, n = 227	placebo, n = 123	OR (95% CI)	
≥5% weight loss, %	48.3	11.4	7.58 (3.71; 15.47)	51.2	13.8	6.41 (3.59; 11.44)	0.72
>10% weight loss, %	21.1	3.0	8.47 (2.52; 28.50)	22.9	4.4	6.49 (2.68; 15.75)	0.73
>15% weight loss, %	4.7	2.9	1.68 (0.45; 6.34)	6.0	2.1	3.17 (0.90; 11.17)	0.50

*Data are based on the full analysis set. Proportions are the proportion achieving categorical fasting weight-loss at week 56, adjusted to the observed baseline distribution of the individuals included in the models in each BMI subgroup. Interaction p values reflect evidence of a difference in treatment effect between BMI subgroups. ORs are liraglutide/placebo.

CI = Confidence interval; OR = odds ratio.

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Limitations

Limitations of this post-hoc analysis include the fact that neither SCALE Obesity and Prediabetes nor SCALE Diabetes was designed or powered for the detection of differences between subgroups and that tests for interaction between treatment group and baseline BMI subgroup have low power in this setting. Further, the tests for interaction between treatment group and baseline BMI subgroup were not adjusted for multiplicity.

Clinical Relevance

A treatment gap exists for individuals with overweight/obesity who do not respond sufficiently to lifestyle interventions and are unable to, or do not wish to, undergo bariatric surgery. Barriers to surgery can include regional variation in healthcare [28], contraindications from comorbidities [29, 30], cost [31], and patient preference for nonsurgical interventions [32, 33]. The increased risks to health and detrimental effects on quality of life associated with BMI ≥ 35 kg/m^2 highlight the importance of finding additional treatment options for these high-risk individuals [5, 34]. Used appropriately, effective prescription drugs in combination with lifestyle interventions could help by filling this weight management treatment gap and provide additional treatment options for individuals for whom currently only few are available [35, 36].

Conclusion

Previously published phase IIIa data have documented the weight-lowering effect of liraglutide 3.0 mg and an acceptable safety profile for weight management in individuals (without [14] and with [15] T2D) with obesity (BMI ≥ 30 kg/m^2) or with overweight (BMI ≥ 27 kg/m^2) plus at least one weight-related comorbidity. The present post-hoc analysis did not show any differences in the treatment effects, or safety profile, of liraglutide 3.0 mg for individuals with a BMI of 27 to <35 or ≥35 kg/m^2. Given the treatment effects of liraglutide 3.0 mg are comparable in individuals with BMI 27 to <35 and ≥35 kg/m^2, liraglutide 3.0 mg can be considered for treatment across the higher as well as lower classes of obesity.

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DOI: 10.1159/000478099

References

1 Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al: Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:766–781.
2 Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al: Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363:2211–2219.
3 Global BMI Mortality Collaboration, Di Angelantonio E, Bhupathiraju Sh N, Wormser D, Gao P, et al: Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016;388:776–786.
4 Sturm R, Hattori A: Morbid obesity rates continue to rise rapidly in the United States. Int J Obes (Lond) 2013;37:889–891.
5 Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH: The disease burden associated with overweight and obesity. JAMA 1999;282:1523–1529.
6 Terranova L, Busetto L, Vestri A, Zappa MA: Bariatric surgery: cost-effectiveness and budget impact. Obes Surg 2012;22:646–653.
7 Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al: 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol 2014;63:2985–3023.
8 American Diabetes Association: Standards of medical care in diabetes-2016 abridged for primary care providers. Clin Diabetes 2016;34:3–21.
9 Lau DC, Douketis JD, Morrison KM, Hramiak IM, Sharma AM, Ur E: 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. CMAJ 2007;176:S1–13.
10 Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al: European guidelines for obesity management in adults. Obes Facts 2015;8:402–424.
11 National Institute for Health and Care Excellence: Surgery for Obese Adults Treatment Pathway. 2016. *http://pathways.nice.org.uk/pathways/obesity#path=view%3A/pathways/obesity/surgery-for-obese-adults.xml* (last accessed September 21, 2017).
12 Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, et al: Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011;34:1481–1486.
13 Novo Nordisk. Saxenda® Highlights of Prescribing Information. 2015. *www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo* (last accessed September 21, 2017).
14 Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al: A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015;373:11–22.
15 Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjoth TV, et al: Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes Randomized Clinical Trial. JAMA 2015;314:687–699.
16 Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, et al: Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes (Lond) 2016;40:1310–1319.
17 Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al: Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond) 2013;37:1443–1451.
18 American Diabetes Association: Standards of medical care in diabetes – 2010. Diabetes Care 2010;33(suppl 1):S11–61.
19 Robinson LE, Holt TA, Rees K, Randeva HS, O'Hare JP: Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: systematic review and meta-analysis. BMJ Open 2013;3: doi: 10.1136/bmjopen-2012-001986.
20 Yoong SL, Carey M, Sanson-Fisher R, Grady A: A systematic review of behavioural weight-loss interventions involving primary-care physicians in overweight and obese primary-care patients (1999–2011). Public Health Nutr 2013;16:2083–2099.
21 Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM: Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension 2003;42:878–884.
22 Aucott L, Poobalan A, Smith WC, Avenell A, Jung R, Broom J: Effects of weight loss in overweight/obese individuals and long-term hypertension outcomes: a systematic review. Hypertension 2005;45:1035–1041.
23 Aucott LS: Influences of weight loss on long-term diabetes outcomes. Proc Nutr Soc 2008;67:54–59.
24 Dalle Grave R, Cuzzolaro M, Calugi S, Tomasi F, Temperilli F, Marchesini G, et al: The effect of obesity management on body image in patients seeking treatment at medical centers. Obesity (Silver Spring) 2007;15:2320–2327.
25 Fontaine KR, Barofsky I, Bartlett SJ, Franckowiak SC, Andersen RE: Weight loss and health-related quality of life: results at 1-year follow-up. Eat Behav 2004;5:85–88.

Obes Facts 2017;10:531–544
DOI: 10.1159/000478099

26 Lean ME, Carraro R, Finer N, Hartvig H, Lindegaard ML, Rossner S, et al: Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults. Int J Obes (Lond) 2014;38:689–697.
27 Wilding JP, Overgaard RV, Jacobsen LV, Jensen CB, le Roux CW: Exposure-response analyses of liraglutide 3.0 mg for weight management. Diabetes Obes Metab 2016;18:491–499.
28 Doumouras AG, Saleh F, Gmora S, Anvari M, Hong D: Regional variations in the public delivery of bariatric surgery: an evaluation of the Center of Excellence Model. Ann Surg 2016;263:306–311.
29 Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres AJ, Weiner R, et al: Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Facts 2013;6:449–468.
30 Society of American Gastrointestinal and Endoscopic Surgeons: Guidelines for Clinical Application of Laparoscopic Bariatric Surgery. 2008. *www.sages.org/publications/guidelines/guidelines-for-clinical-application-of-laparoscopic-bariatric-surgery/* (last accessed September 21, 2017).
31 Korda RJ, Joshy G, Jorm LR, Butler JR, Banks E: Inequalities in bariatric surgery in Australia: findings from 49,364 obese participants in a prospective cohort study. Med J Aust 2012;197:631–636.
32 Sikorski C, Luppa M, Dame K, Brahler E, Schutz T, Shang E, et al: Attitudes towards bariatric surgery in the general public. Obes Surg 2013;23:338–345.
33 Funk LM, Jolles S, Fischer LE, Voils CI: Patient and referring practitioner characteristics associated with the likelihood of undergoing bariatric surgery: a systematic review. JAMA Surg 2015;150:999–1005.
34 Ul-Haq Z, Mackay DF, Fenwick E, Pell JP: Meta-analysis of the association between body mass index and health-related quality of life among adults, assessed by the SF-36. Obesity (Silver Spring) 2013;21:E322–327.
35 Gesundheit N: Filling the treatment gap in the weight management of overweight and obese patients. Int J Obes Suppl 2012;2(suppl 1):S39–S42.
36 Department of Health Policy School of Public Health and Health Services, The George Washington University: Obesity Drug Outcome Measures 201*http://publichealth.gwu.edu/pdf/obesitydrugmeasures.pdf* (last accessed September 21, 2017).