Diabetes Ther (2023) 14:1867–1887
https://doi.org/10.1007/s13300-023-01457-7

ORIGINAL RESEARCH

Improved Glycaemic and Weight Management Are Associated with Better Quality of Life in People with Type 2 Diabetes Treated with Tirzepatide

Kristina S. Boye · Hélène Sapin · Wenxiu Dong · Suzanne Williamson · Clare J. Lee · Vivian Thuyanh Thieu

Received: June 20, 2023 / Accepted: July 27, 2023 / Published online: September 5, 2023

ABSTRACT

Introduction: Limited data are available on the relationship between quality of life (QoL) change and significant degrees of reduction in glycated haemoglobin (HbA1c) and/or weight loss in people with type 2 diabetes (T2D). We explored the associations between HbA1c targets and/or weight loss achieved and patient-reported outcomes (PROs) in adults with T2D treated with tirzepatide, a first-in-class once weekly glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, using pooled data from SURPASS-1 to -5 Phase 3 clinical trials.

Methods: PROs were assessed using five instruments at baseline and endpoint (Week 40 in SURPASS-1, -2 and -5; Week 52 in SURPASS-3 and -4): Impact of Weight on Quality of Life-Lite Clinical Trials Version; Impact of Weight on Self-Perception (IW-SP) questionnaire; Ability to Perform Physical Activities of Daily Living (APPADL); Diabetes Treatment Satisfaction Questionnaire change; and EQ-5D-5L. All PROs were assessed in participants receiving pooled doses of tirzepatide (5, 10 or 15 mg) and achieving HbA1c targets of $< 5.7\%$, ≥ 5.7–$\leq 6.5\%$ and $> 6.5\%$ or achieving ≥ 0–$< 5\%$, ≥ 5–$< 10\%$, ≥ 10–$< 15\%$ and $\geq 15\%$ weight loss from baseline at endpoint. The APPADL, IW-SP and EQ visual analogue scores were evaluated in participants achieving each combination of HbA1c target and weight loss.

Results: Achievement of lower HbA1c targets or higher body weight percentage losses were each associated with greater improvements in QoL than achievement of higher HbA1c targets or lower body weight percentage losses, respectively. Achievement of lower HbA1c targets in combination with greater weight loss was generally associated with the best QoL ratings.

Conclusions: Our findings demonstrate that HbA1c targets and significant percentage body weight reduction thresholds need to be achieved for people with T2D to help substantially increase their overall health-related QoL. Tirzepatide treatment may allow a high

Prior Presentation This manuscript is based on work that has previously been presented in posters at The International Diabetes Federation World Congress, 5–8 December 2022 in Lisbon, Portugal.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-023-01457-7.

K. S. Boye (✉) · H. Sapin · C. J. Lee · V. T. Thieu
Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA
e-mail: boye_kristina_secnok@lilly.com

W. Dong
TechData Service Company, King of Prussia, PA, USA

S. Williamson
Greenwich HE&OR Ltd., London, UK

proportion of people with T2D to achieve these targets, enabling improved QoL.
Clinical Trial Registration: SURPASS-1: NCT03954834; SURPASS-2: NCT03987919; SURPASS-3: NCT03882970; SURPASS-4: NCT03730662; SURPASS-5: NCT04039503.

PLAIN LANGUAGE SUMMARY

Limited data exist about the relationship between quality of life (QoL) and changes in clinical measures, for example management of blood sugar levels and weight, in people with type 2 diabetes. We explored the associations between glucose and weight loss targets achieved and QoL outcomes reported by adults treated with tirzepatide, the first glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist approved for the treatment of people with type 2 diabetes, using data from SURPASS-1 to -5 Phase 3 clinical trials.

Five questionnaires, developed to evaluate patients' health-related QoL, were completed by patients at the beginning and end of the clinical trials, which was after 40 weeks for SURPASS-1, -2 and -5 and after 52 weeks for SURPASS-3 and -4, or when the person left the trial if this was before the official end. These questionnaires were: EQ-5D-5L (SURPASS-1 to -5); Impact of Weight on Self-Perception questionnaire (SURPASS-1 to -5); Ability to Perform Physical Activities of Daily Living (SURPASS-1 to -5); Diabetes Treatment Satisfaction Questionnaire change (SURPASS-2 to -5); and Impact of Weight on Quality of Life-Lite Clinical Trials Version (SURPASS-2 only).

Overall, achievement of lower glucose targets or higher percentage of body weight losses were each associated with greater improvements in QoL. Achievement of lower glucose targets in combination with greater weight loss was generally associated with the highest health-related QoL ratings.

Tirzepatide treatment may allow a high proportion of people with type 2 diabetes to achieve lower glucose levels and higher weight loss, enabling improved health-related QoL.

Keywords: HbA1c; Patient-reported outcomes; Quality of life; SURPASS; Tirzepatide; Type 2 diabetes; Weight loss

Key Summary Points

Why carry out this study?

In addition to glycaemic management, the American Diabetes Association recommends weight loss for people with type 2 diabetes with overweight or obesity; however, few data are available on the relationship between health-related quality of life change and different degrees of reduction in glycated haemoglobin (HbA1c) and/or weight loss in this population.

We present data on the associations between HbA1c targets and/or weight loss achieved and patient-reported outcomes in adults treated with tirzepatide, a novel once weekly glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist approved for the treatment of people with type 2 diabetes, using pooled data from the SURPASS-1 to -5 Phase 3 clinical trials.

What was learned from the study?

Achievement of lower HbA1c targets or higher percentage of body weight losses was each associated with greater improvements in quality of life among adults receiving any dose of tirzepatide (5, 10 or 15 mg) in SURPASS-1 to -5 than achievement of higher HbA1c targets or lower percentage of body weight losses, respectively. Achievement of lower HbA1c targets in combination with greater weight loss was generally associated with the highest health-related quality of life ratings.

These findings demonstrate that HbA1c targets and adequate percentage body weight reduction thresholds need to be achieved for people with type 2 diabetes to help substantially increase their overall health-related quality of life.

INTRODUCTION

Glucose-lowering medications (GLMs) combined with healthy lifestyle changes are recommended to achieve glycaemic targets in the treatment of type 2 diabetes (T2D) [1]. In addition to glycaemic management, the American Diabetes Association (ADA) recommends weight loss $\geq$ 5% for people with T2D with overweight or obesity [2]. However, higher weight loss goals (> 10%) are clinically relevant, particularly for those with a body mass index (BMI) of $\geq$ 35 kg/m^2, given the evidence for further benefits in reducing cardiovascular risk and obesity-related comorbidities [3, 4].

T2D is a progressive disease and maintaining glycaemic and weight management over time often requires treatment intensification [1, 5]. Tirzepatide, a first-in-class once weekly glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, is approved for treatment of people with T2D [6, 7] and is under investigation for chronic weight management. In the SURPASS-1 to -5 Phase 3 clinical trials, tirzepatide resulted in statistically significant and clinically meaningful reductions in glycated haemoglobin (HbA1c), enabling many people with T2D to achieve HbA1c < 5.7% [8] and substantial weight reduction [9–13].

The medical management of T2D, along with lifestyle changes, has consequences for the patient's quality of life (QoL); therefore, the measurement of health-related patient-reported outcomes (PROs) in clinical trials of new medications is increasingly being recognised as of importance. For example, the Institute for Clinical and Economic Review 'Tirzepatide for Type 2 Diabetes: Final Policy Recommendations' published in 2022 stated that the 'inclusion of several validated QoL measures…are to be commended and should be replicated by all manufacturers when designing trials testing new therapies to treat T2D' [14]. PRO measures complement clinical assessments, providing additional information to support decision-making regarding the right treatment strategy for an individual with T2D. In fact, current ADA guidance recommends that patient preference and experience play a major role in decisions made by healthcare providers (HCPs) and should form part of the discussion when choosing a treatment for individual patients [15]. However, little research has been published in terms of the relationship between QoL change and degrees of reduction in HbA1c and/or weight loss in patients with T2D.

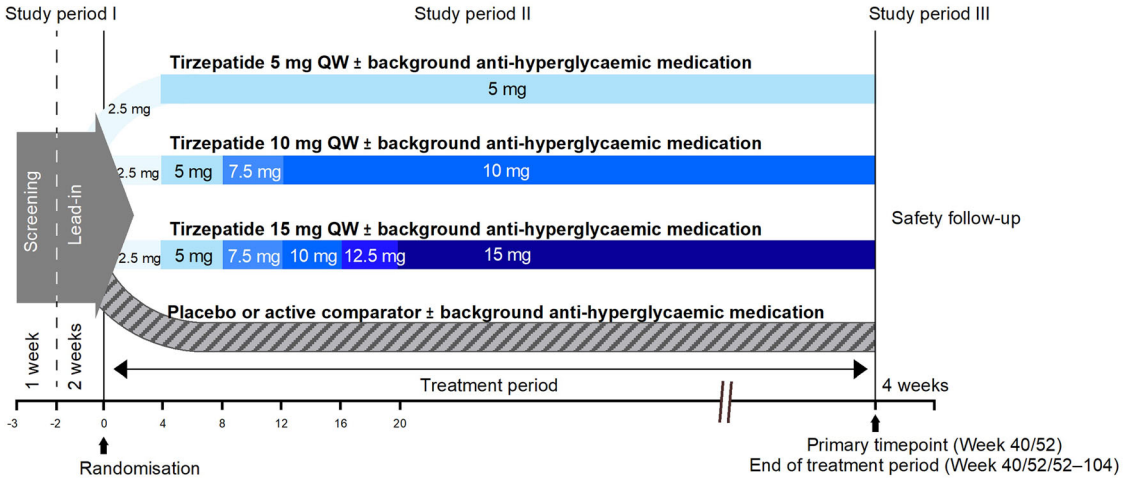
Improvements in PROs were observed in people with T2D treated with tirzepatide 5, 10 or 15 mg across the SURPASS-1 to -5 Phase 3 clinical trials [16]. Furthermore, a recent study found a statistically significant but modest correlation between HbA1c and body weight change with tirzepatide treatment in people with T2D in several SURPASS studies, suggesting that both weight-independent and -dependent mechanisms are responsible for improvements in glycaemic improvements induced by tirzepatide [17]. Therefore, our objective was to explore the associations between HbA1c targets and/or weight loss achieved and PROs in adults with T2D treated with tirzepatide 5, 10 or 15 mg using pooled data from the SURPASS-1 to -5 Phase 3 clinical trials, thus making a unique contribution to the literature in T2D. PRO data for the individual tirzepatide dose groups and all comparators from the SURPASS-1 to -5 Phase 3 clinical trials have been published in detail elsewhere [16].

METHODS

Participants and Study Design

Details of each of the five SURPASS clinical trials used for this analysis, including key inclusion and exclusion criteria, have been published elsewhere [9–13]. In brief, SURPASS-1 to -5 were Phase 3, randomised, parallel group, multinational trials of 40- or 52-weeks treatment duration that compared the efficacy and safety of once weekly tirzepatide 5, 10 or 15 mg administered by subcutaneous injection versus placebo or active comparator in adults with T2D at Week 40 (SURPASS-1, -2 and -5) or Week 52 (SURPASS-3 and -4) as the primary endpoint. A summary of the design of these studies is included in Fig. 1.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Study protocols were approved by local ethics review boards, and all participants provided written informed consent. All studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines [18].



Randomised, parallel, multicentre study (design)	Randomisation ratio, comparator	Background GLM	Tirzepatide sample size	Primary timepoint
SURPASS-1 (double-blind, placebo-controlled)	1:1:1:1, placebo once weekly	None	N=363	Week 40
SURPASS-2 (open-label, active-controlled)	1:1:1:1, semaglutide 1 mg once weekly	Metformin	N=1,409	Week 40
SURPASS-3 (open-label, active-controlled)	1:1:1:1, titrated insulin degludec once daily	Metformin ± SGLT-2i	N=1,077	Week 52
SURPASS-4 (open-label, active-controlled)	1:1:1:3, titrated insulin glargine once daily	Metformin and/or SU and/or SGLT-2i	N=995	Week 52
SURPASS-5 (double-blind, placebo-controlled)	1:1:1:1, placebo once weekly	Titrated insulin glargine ± metformin	N=355	Week 40

Fig. 1 SURPASS-1 to -5 Phase 3 clinical trial study design. Analyses were conducted on the modified intent-to-treat efficacy data set composed of all randomly assigned participants exposed to at least one dose of tirzepatide and assigned to tirzepatide at randomisation regardless of the treatment received. Observations occurring after rescue therapy with another GLM or treatment discontinuation were excluded. For patients with missing values at endpoint, last observation prior to treatment discontinuation or rescue therapy was carried forward. *GLM* glucose-lowering medication, *N* number of subjects, *QW* once weekly, *SGLT-2i* sodium-glucose co-transporter-2 inhibitor, *SU* sulphonylurea

PRO Measures

PROs were assessed using five instruments in the SURPASS-1 to -5 Phase 3 clinical trials (see Table 1), which have been described in detail in a previous publication [16]. Overall health-related QoL was measured using the EQ-5D-5L instrument [19], while treatment satisfaction was evaluated using the Diabetes Treatment Satisfaction Questionnaire change (DTSQc) [20]. Different concepts associated with weight-related QoL were measured using three further instruments: Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) [21], Impact of Weight on Self-Perception (IW-SP) questionnaire [22] and Ability to Perform Physical Activities of Daily Living (APPADL) [23, 24].

The PRO instruments selected for each SURPASS clinical trial were determined by the overall study characteristics and availability of the measures at the time of protocol approval. Therefore, not all PROs were included in all five studies; the IWQOL-Lite-CT was only utilised in SURPASS-2 and the DTSQc was only used in SURPASS -2 to -5. The EQ-5D-5L, IW-SP and APPADL were utilised in SURPASS-1 to -5.

PROs were assessed at baseline and endpoint (Week 40 for SURPASS-1, -2 and -5; Week 52 for SURPASS-3 and -4) or early discontinuation and were scored according to the developer's guidelines. In the presence of missing items, calculation of PRO scores was handled according to the developer's instructions. Higher PRO scores indicate better outcomes for all measures [19–24], except the DTSQc hypoglycaemia and hyperglycaemia scores, for which lower scores indicate a decrease in perceived frequency of time of unacceptably low or high blood glucose, respectively (Table 1) [20]. Higher EQ-5D-5L index, EQ visual analogue scale (VAS) and DTSQc total treatment satisfaction scores indicate higher health utility, better self-rated health status and greater improvements in treatment satisfaction, respectively [19, 20]. In terms of weight-related QoL, higher IWQOL-Lite-CT, IW-SP and APPADL scores indicate higher levels of functioning associated with weight, better self-perception in relation to weight and better self-reported APPADL, respectively (Table 1) [21–24].

Outcomes Described

In these analyses, all PROs included in SURPASS-1 to -5 were assessed in participants receiving any dose of tirzepatide (5, 10 or 15 mg) and achieving HbA1c (%) targets of $< 5.7\%$ (the clinical threshold defining normal blood glucose), ≥ 5.7 to $\leq 6.5\%$ (the clinical range defining pre-diabetes) and $> 6.5\%$ (the clinical threshold defining diabetes) at study endpoint [8]. In addition, all PROs were evaluated in participants receiving any dose of tirzepatide and achieving percentage reductions of ≥ 0.5 to $< 1.0\%$, ≥ 1.0 to $< 1.5\%$, ≥ 1.5 to $< 2.0\%$ and $\geq 2.0\%$ in HbA1c (%) from baseline at study endpoint to account for variations in baseline HbA1c (%) values.

Regarding weight loss, all PROs included in SURPASS-1 to -5 were assessed in participants receiving any dose of tirzepatide (5, 10 or 15 mg) and achieving ≥ 0 to $< 5\%$, ≥ 5 to $< 10\%$, ≥ 10 to $< 15\%$ and $\geq 15\%$ weight loss from baseline at study endpoint. Furthermore, to explore the relationship between HbA1c (%), weight loss and QoL, selected weight-related PROs without ceiling effects (IW-SP and APPADL) and self-rated health status (EQ VAS) were evaluated in SURPASS-1 to -5 participants receiving any dose of tirzepatide and achieving each combination of HbA1c (%) target ($< 5.7\%$, ≥ 5.7 to $\leq 6.5\%$ and $> 6.5\%$) and weight loss (≥ 0 to $< 5\%$, ≥ 5 to $< 10\%$, ≥ 10 to $< 15\%$ and $\geq 15\%$) from baseline at study endpoint.

Statistical Methods

Data from all participants treated with tirzepatide in the five studies were pooled, regardless of dosage; therefore, the pooled treatment group included participants receiving tirzepatide 5, 10 or 15 mg in SURPASS-1 to -5. Statistical analyses were performed on the modified intent-to-treat population efficacy data set composed of all randomly assigned participants exposed to at least one dose of tirzepatide regardless of the treatment received. Participants who

Table 1 Overview of the patient-reported outcome measures administered in the SURPASS-1 to -5 Phase 3 clinical trials

Measure	Component measures	Description	Items	Scoring	Interpretation of scoring
Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) [21, 31]	Total score	Measure of weight-related functioning in populations commonly targeted for clinical trials of new weight loss medications	Twenty items (see below) each rated on a 5-point scale from 1 'never/not at all true' to 5 'always/completely true'	Scored from 0 to 100	Higher total score indicates higher level of functioning associated with weight No MID published Higher composite scores indicate higher levels of functioning in specific domains associated with weight
	Physical (composite score)		Primary domain–seven items: • Trouble bending over • Tired or winded • Unable to stand comfortably • Not physically active • Unable to walk far/quickly • Uncomfortable in small seats • Bodily pain		
	Physical function (composite score)		Five of the seven items comprising Physical (composite score): • Trouble bending over • Tired or winded • Unable to stand comfortably • Not physically active unable to walk far/quickly		
	Psychosocial (composite score)		Primary domain–13 items: • Self-conscious eating in social settings • Less confident • Feel judged by others • Frustrated shopping for clothes • Feel bad or upset about pictures of self		

Table 1 continued

Measure	Component measures	Description	Items	Scoring	Interpretation of scoring
				• Down or depressed about weight • Less interested in sexual activity • Avoid social gatherings • Less productive • Lack energy • Worried about health • Self-conscious about weight • Frustrated or upset about weight	
Impact of Weight on Self-Perception (IW-SP) questionnaire [22]		Measure of patients' self-perception relating to their body weight	Three items: • Feel unhappy with appearance due to weight • Feel self-conscious in public due to weight • Feel unhappy due to comparing weight with others Each rated on a 5-point scale from 1 'always' to 5 'never'	Averaged and linearly transformed to produce a score from 0 to 100	Higher raw and transformed scores indicate better self-perception in relation to weight MID = 25 points (transformed score) [32]
Ability to Perform Physical Activities of Daily Living (APPADL) [23, 24]		Measure of self-reported ability to perform tasks of daily living	Seven items: • Getting up from floor/ground • Getting down to floor/ground • Standing • Climbing stairs • Household chores/yard work • Moderate physical activity • Strenuous physical activity Each scored on a 5-point numeric rating scale from 1 'unable to do' to 5 'not at all difficult'	Raw scores, derived by summing the item scores and dividing by the number of items, are linearly transformed to a score from 0 to 100	Higher raw and transformed scores indicate better self-reported APPADL MID = 6–14 points (transformed score)

Table 1 continued

Measure	Component measures	Description	Items	Scoring	Interpretation of scoring
Diabetes Treatment Satisfaction Questionnaire change (DTSQc) [20, 33]	Total treatment satisfaction	Measure of change in satisfaction with current treatment compared to baseline	Six items: • Satisfied with current treatment • Feel convenient about recent treatment • Feel flexible about recent treatment • Satisfied with diabetes understanding • Recommend present treatment to others • Continue with present treatment Each scored on a 7-point scale from −3 'much less satisfied now' to +3 'much more satisfied now'	Scored from −18 to +18	Higher scores indicate greater improvements in treatment satisfaction A score of 0 indicates no change No MID published
	Hypoglycaemia	Measure of change in perceived frequency of hypoglycaemia compared to baseline	One item: • Times of unacceptably low blood glucose Scored on a 7-point scale from −3 'much less of the time now' to +3 'much more of the time now'	Scored from −3 to +3	Higher scores indicate an increase in perceived frequency of hypoglycaemia A score of 0 indicates no change
	Hyperglycaemia	Measure of change in perceived frequency of hyperglycaemia compared to baseline	One item: • Times of unacceptably high blood glucose Scored on a 7-point scale from −3 'much less of the time now' to +3 'much more of the time now'	Scored from −3 to +3	Higher scores indicate an increase in perceived frequency of hyperglycaemia A score of 0 indicates no change

Table 1 continued

Measure	Component measures	Description	Items	Scoring	Interpretation of scoring
EQ-5D [19]	EQ-5D-5L index score	Measure of health status	Five dimensions: • Mobility • Self-care • Usual activities • Pain/discomfort • Anxiety/depression Each with five levels of response: • No problems • Slight problems • Moderate problems • Severe problems • Unable to/extreme problems	UK-based utility index score calculated using a crosswalk algorithm that maps EQ-5D-5L to EQ-5D-3L value sets [34] Scored from −0.59 to 1	Higher scores indicate higher health utility A score of 1 indicates perfect health, 0 indicates death and negative scores represent values worse than death MID = 0.03–0.0549 [35]
	EQ VAS	Records respondent's self-rated health status	Records the respondent's overall current health on a vertical scale	Scored from 0 to 100	Higher scores indicate better self-rated health status A score of 0 indicates worst imaginable health, 100 indicates best imaginable health

MID minimally important difference, *VAS* visual analogue scale

discontinued tirzepatide because of inadvertent study enrolment, with missing baseline or endpoint HbA1c (%) or weight data, as appropriate, or with missing baseline PRO value and/or without ≥ 1 post-baseline PRO value were excluded. Observations occurring after rescue therapy with another GLM or treatment discontinuation were excluded (efficacy estimand).

Baseline demographic and clinical characteristics were summarised descriptively: mean (standard deviation [SD]) for continuous data and *n* (%) for categorical data. *p*-values presented for pooled SURPASS-1 to -5 participants by HbA1c categories and weight loss categories achieved at endpoints, when applicable, were calculated using analysis of variance (ANOVA) for continuous data and Chi-square test for categorical data.

Change from baseline was calculated for all HbA1c (%) target, percentage HbA1c (%) reduction and weight loss categories across all PRO instruments. The last post-baseline observation prior to treatment discontinuation or rescue therapy was carried forward to impute missing post-baseline values. Descriptive statistics were calculated for the PRO variables: mean, SD and 95% confidence intervals (CIs) for continuous variables; absolute and relative frequencies for categorical variables.

Additional analyses using an analysis of covariance (ANCOVA) model adjusted for baseline clinical characteristics, including gender (weight analyses only), duration of T2D, antihyperglycaemic drug use, fasting serum glucose, PRO value and HbA1c (%) concentration or weight (kg), as appropriate, were undertaken to account for differences at baseline between participants in HbA1c (%) target achieved and weight loss categories at endpoint. All statistical analyses were performed using SAS, version 9.4 (The SAS Institute, Cary, NC, USA).

RESULTS

Baseline Demographic and Clinical Characteristics

Overall, 4199 adults with T2D were treated with once weekly tirzepatide 5, 10 or 15 mg in the SURPASS-1 to -5 Phase 3 clinical trials. Statistically significant differences in several baseline demographic and clinical characteristics were observed between tirzepatide-treated participants in different HbA1c (%) target achieved at endpoint categories and between tirzepatide-treated participants in different endpoint weight loss categories at endpoint (Table 2). Participants achieving HbA1c < 5.7% at endpoint were younger, had lower baseline HbA1c (%) and fasting serum glucose levels, and shorter duration of disease compared with participants with HbA1c ≥ 5.7% at endpoint. Similarly, participants achieving greater weight loss at endpoint (i.e. ≥ 15% weight loss from baseline) were younger, were more likely to be female, had lower baseline HbA1c (%), had lower fasting serum glucose levels and had lower baseline weight compared with participants in lesser weight loss categories at endpoint (i.e. < 15% weight loss from baseline). Table S1 in the electronic Supplementary Material reports baseline demographic and clinical characteristics by category of percentage reduction in HbA1c (%) achieved from baseline to endpoint.

Association Between HbA1c Levels and PROs

At endpoint, improvements from baseline were observed for all PRO measures across all HbA1c (%) target achieved categories (< 5.7%, ≥ 5.7 to ≤ 6.5% and > 6.5%), indicating enhanced QoL after initiation of tirzepatide (Fig. 2). Achievement of lower HbA1c (%) targets at endpoint was generally associated with greater improvements in PRO measures compared with achievement of higher HbA1c (%) targets. For example, improvements in IWQOL-Lite-CT composite and total scores, IW-SP and APPADL total scores increased as lower endpoint HbA1c (%) targets were achieved, with the largest improvements from baseline being observed in participants achieving HbA1c < 5.7% at endpoint (Fig. 2A–C). Higher DTSQc total scores at endpoint were observed for those participants achieving HbA1c < 5.7% and ≥ 5.7 to ≤ 6.5% targets at endpoint compared with those

Table 2 Baseline demographic and clinical characteristics of adults with T2D treated with tirzepatide (any dose) in SURPASS-1 to -5 by HbA1c (%) target achieved at endpoint and weight loss category at endpoint

	Pooled tirzepatide patients								
	Achieving HbA1c (%) target at endpoint				**Achieving weight loss at endpoint**				
	< 5.7% *n* = 1476	**≥ 5.7% to ≤ 6.5% *n* = 1697**	**> 6.5% *n* = 1016**	***p*-value**	**≥ 0 to < 5% *n* = 907**	**≥ 5 to < 10% *n* = 1087**	**≥ 10 to < 15% *n* = 923**	**≥ 15% *n* = 966**	***p*-value**
Age (years)	56.6 (10.4)	59.4 (10.1)	59.8 (10.4)	< 0.001	58.8 (10.7)	58.5 (10.2)	59.4 (9.9)	57.6 (10.5)	0.002
Female, *n* (%)	695 (47.1)	781 (46.0)	475 (46.8)	0.945	361 (39.8)	455 (41.9)	418 (45.3)	585 (60.6)	< 0.001
Race, *n* (%)				0.057					0.006
White	1181 (80.0)	1349 (79.5)	800 (78.8)		704 (77.6)	828 (76.3)	757 (82.0)	790 (81.8)	
Asian	129 (8.7)	126 (7.4)	57 (5.6)		80 (8.8)	86 (7.9)	54 (5.9)	81 (8.4)	
American Indian or Alaska Native	117 (7.9)	134 (7.9)	96 (9.5)		77 (8.5)	118 (10.9)	69 (7.5)	63 (6.5)	
Black or African American	36 (2.4)	74 (4.4)	51 (5.0)		40 (4.4)	44 (4.1)	35 (3.8)	21 (2.2)	
Multiple	12 (0.8)	10 (0.6)	9 (0.9)		4 (0.4)	8 (0.7)	7 (0.8)	9 (0.9)	
Native Hawaiian or Other Pacific Islander	1 (0.1)	3 (0.2)	2.(0.2)		2 (0.2)	1 (0.1)	1 (0.1)	2 (0.2)	
Not reported	0	1 (0.1)	1 (0.1)		0	2 (0.2)	0	0	
HbA1c (%) concentration	8.05 (0.92)	8.29 (0.91)	8.64 (1.00)	< 0.001	8.42 (1.00)	8.34 (1.00)	8.23 (0.91)	8.14 (0.89)	< 0.001
Fasting serum glucose (mg/dl)	164.6 (49.7)	168.5 (46.1)	180.6 (55.9)	< 0.001	173.9 (53.0)	171.4 (52.7)	170.5 (48.1)	163.4 (45.4)	< 0.001
Duration of T2D (years)	8.0 (6.6)	9.7 (7.0)	10.7 (7.4)	< 0.001	9.8 (7.0)	9.1 (6.7)	9.6 (7.1)	9.2 (7.4)	0.078
BMI (kg/m^2)	33.6 (6.2)	33.5 (6.4)	33.0 (6.3)	0.184	33.6 (6.5)	33.2 6.6)	33.0 (5.7)	33.8 (6.5)	0.011
Weight (kg)	93.1 (20.1)	92.8 (21.1)	91.4 (20.6)	0.227	94.3 (21.9)	92.6 (20.7)	91.9 (19.3)	91.4 (20.6)	0.013

Any dose = 5, 10 or 15 mg administered by subcutaneous injection once weekly

Data reported are mean (standard deviation) unless otherwise indicated

n = number of participants in HbA1c or weight loss category at endpoint

p-values calculated using ANOVA for continuous data and Chi-square test for categorical data

ANOVA analysis of variance, *BMI* body mass index, *HbA1c* glycated haemoglobin, *T2D* type 2 diabetes

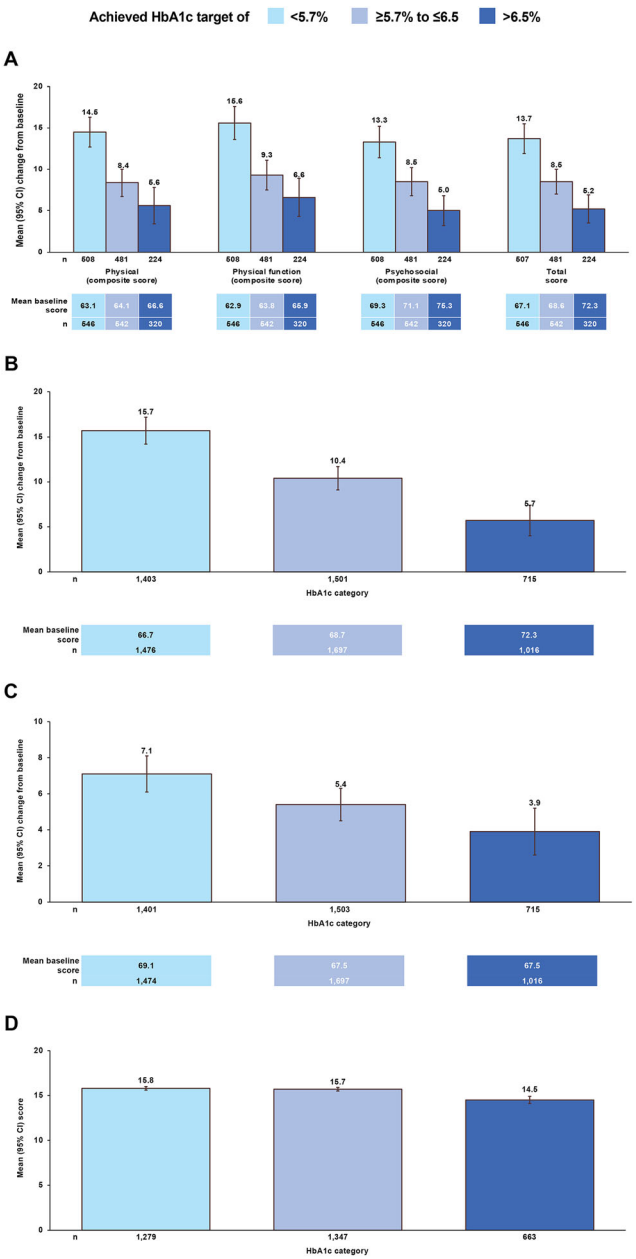


Fig. 2 PROs for adults with type 2 diabetes treated with tirzepatide (any dose*) achieving HbA1c (%) targets of < 5.7%, ≥ 5.7% to ≤ 6.5% or > 6.5% at endpoint in SURPASS-1 to -5. **A** Changes from baseline in IWQOL-Lite-CT composite and total scores at endpoint. **B** Changes from baseline in IW-SP total score† at endpoint. **C** Changes from baseline in APPADL total score† at endpoint. **D** Endpoint DTSQc total treatment satisfaction scores. **E** Endpoint DTSQc hypoglycaemia and hyperglycaemia scores. **F** Changes from baseline in EQ-5D-5L index score at endpoint. **G** Changes from baseline in EQ VAS at endpoint. *Any dose = 5, 10 or 15 mg administered by subcutaneous injection once weekly. † Transformed IW-SP and APPADL scores presented above have been linearly transformed from raw scores to a scale of 0–100. IWQOL-Lite-CT was only measured in SURPASS-2. DTSQc was only measured in SURPASS-2 to -5. All other PROs were measured in all five SURPASS studies. *APPADL* Ability to Perform Physical Activities of Daily Living, *CI* confidence interval, *DTSQc* Diabetes Treatment Satisfaction Questionnaire change, *HbA1c* glycated haemoglobin, *IWQOL-Lite-CT* Impact of Weight on Quality of Life-Lite Clinical Trials Version, *IW-SP* Impact of Weight on Self-Perception, *PRO* patient-reported outcome, *VAS* visual analogue scale

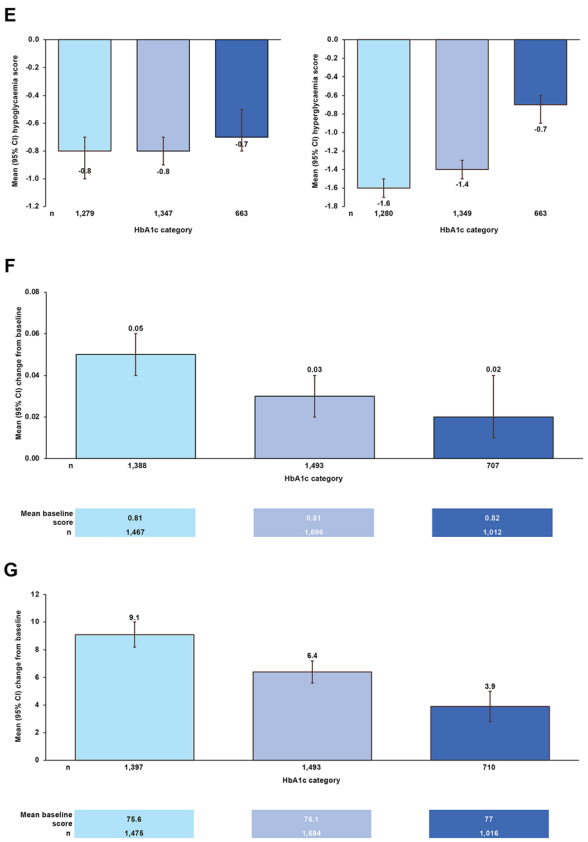


Fig. 2 continued

achieving HbA1c > 6.5% (Fig. 2D). Although DTSQc hypoglycaemia scores at endpoint were similar across all HbA1c (%) target categories, improvements in DTSQc hyperglycaemia scores were observed as lower endpoint HbA1c (%) targets were achieved (Fig. 2E). Improvements in EQ-5D-5L index score and EQ VAS also increased as lower endpoint HbA1c (%) targets were achieved (Fig. 2F, G). Results of the ANCOVA analyses by HbA1c (%) target achieved at endpoint for all PROs, adjusted according to baseline characteristics, were generally aligned with those of the descriptive analyses (Table S2 in the electronic Supplementary Material). Moreover, analyses of all PROs in participants receiving any dose of tirzepatide and achieving percentage reductions of ≥ 0.5 to < 1.0%, ≥ 1.0 to < 1.5%, ≥ 1.5 to < 2.0% and ≥ 2.0% in HbA1c (%) from baseline showed similar results; reduction in HbA1c level was associated with improved weight-related and overall QoL, with greater improvement generally observed in participants achieving larger HbA1c reductions (Fig. S1 in the electronic Supplementary Material).

Association Between Weight Loss and PROs

Improvements from baseline to endpoint were also observed for all PRO measures across all weight loss categories, confirming enhanced QoL after initiation of tirzepatide (pooled doses) (Fig. 3). Greater weight loss at endpoint was generally associated with larger improvements in PRO measures compared with lesser weight loss. Improvements in IWQOL-Lite-CT composite and total scores, IW-SP and APPADL total scores increased as greater weight loss at endpoint was achieved; the largest improvements from baseline were observed in participants achieving ≥ 15% weight loss at endpoint (Fig. 3A–C). Higher DTSQc total scores at endpoint were observed for participants in the ≥ 10 to < 15% and ≥ 15% weight loss categories at endpoint compared with those in the lowest weight loss category (≥ 0 to < 5% weight loss from baseline) (Fig. 3D). DTSQc hypoglycaemia and hyperglycaemia scores at endpoint tended to improve with increasing weight loss, although this trend was not consistent in the highest weight loss category (≥ 15% weight loss from baseline) (Fig. 3E). Changes from baseline in EQ-5D-5L index scores were greater in the highest weight loss category (≥ 15% weight loss from baseline) compared with the lower weight loss categories (≥ 0 to < 5% and ≥ 5 to < 10%) (Fig. 3F). Furthermore, changes from baseline in EQ VAS were greater with increasing weight loss at endpoint, indicating better self-rated health status for tirzepatide-treated participants achieving the greatest weight loss (Fig. 3G). Results of the ANCOVA analyses by weight loss category at endpoint for all PROs, adjusted according to baseline characteristics, were generally aligned with those of the descriptive analyses (Table S2 in the electronic Supplementary Material).

Associations Among HbA1c Levels, Weight Loss and Weight-Related PROs

Overall, the trends in PROs observed in the separate HbA1c (%) target and weight loss analyses described above were generally observed in the three-way analyses of selected PROs in SURPASS-1 to -5 participants receiving any dose of tirzepatide and achieving each combination of HbA1c (%) target ($< 5.7\%$, ≥ 5.7 to $\leq 6.5\%$ and $> 6.5\%$) and weight loss category (≥ 0 to $< 5\%$, ≥ 5 to $< 10\%$, ≥ 10 to $< 15\%$ and $\geq 15\%$) from baseline, although small sample sizes in some combination categories resulted in wide CIs (Fig. 4). Achievement of lower HbA1c (%) targets in combination with greater weight loss at endpoint was generally associated with larger improvements in PRO measures compared with achievement of higher HbA1c (%) targets and lesser weight loss.

The largest improvements from baseline to endpoint in IW-SP total score were observed for participants achieving HbA1c $< 5.7\%$ or ≥ 5.7 to $\leq 6.5\%$ targets and $\geq 15\%$ weight loss at endpoint (Fig. 4A). Regarding changes from baseline in APPADL total score, the trend in terms of weight loss observed in the two-way analyses described above remained strong, with improvements in self-reported APPADL increasing with greater weight loss at endpoint; however, the association with HbA1c (%) target achieved at endpoint was less visible, potentially because of outliers and/or small sample sizes in some combination categories (Fig. 4B). Changes from baseline in self-rated health status, as measured by EQ VAS, increased as lower HbA1c (%) targets and greater weight loss were achieved, although the effect of weight loss appeared to be lost among those patients in the HbA1c $> 6.5\%$ target category (Fig. 4C). The largest improvements from baseline to endpoint in EQ VAS were observed for participants achieving HbA1c $< 5.7\%$ and $\geq 15\%$ weight loss at endpoint, with all tirzepatide-treated participants who achieved HbA1c $< 5.7\%$ at endpoint showing greater improvements in self-rated health status than those achieving HbA1c ≥ 5.7 to $\leq 6.5\%$ or $> 6.5\%$ targets, within each weight loss category at endpoint.

DISCUSSION

We have described associations for achieved HbA1c targets and/or weight loss categories with PROs evaluating overall QoL, treatment satisfaction and patient perspectives on weight-related attributes in people with T2D treated with 5, 10 or 15 mg tirzepatide in the SURPASS-1 to -5 Phase 3 clinical trials. Overall, once weekly tirzepatide 5, 10 or 15 mg improved outcomes across all PROs measured at study endpoint, indicating improvements in functioning associated with weight, self-perception in relation to weight, self-reported APPADL, self-rated health status and satisfaction with treatment.

In SURPASS-1 to -5, glycaemic improvement was associated with improved PROs, with the greatest improvement observed in participants achieving lower HbA1c (%) targets with tirzepatide treatment. Although current guidelines on the management of T2D recommend an HbA1c goal of $< 7\%$ without significant hypoglycaemia for many non-pregnant adults, they also state that achievement of even lower HbA1c levels may be acceptable and even beneficial if it can be achieved safely and judged appropriate by the treating HCP and preferred by the patient [25], thereby also highlighting the importance now placed on the patients' perspective and engagement with disease management in achieving better clinical outcomes.

As a first-in-class GIP/GLP-1 receptor agonist, the first new class of diabetes medication introduced in nearly a decade [6, 26], tirzepatide treatment has resulted in statistically significant and clinically meaningful reductions in HbA1c and weight loss compared to placebo and several active comparators in clinical trials, including semaglutide, a selective GLP-1 receptor agonist [9–13]. Furthermore, across all five studies, treatment with tirzepatide 5, 10 or 15 mg resulted in greater improvements in people's QoL at the end of the study compared with placebo or treatment with the comparators [16], The results of our analyses suggest therefore that the ability of tirzepatide to reduce HbA1c so that targets are achieved by a greater proportion of people with T2D than has

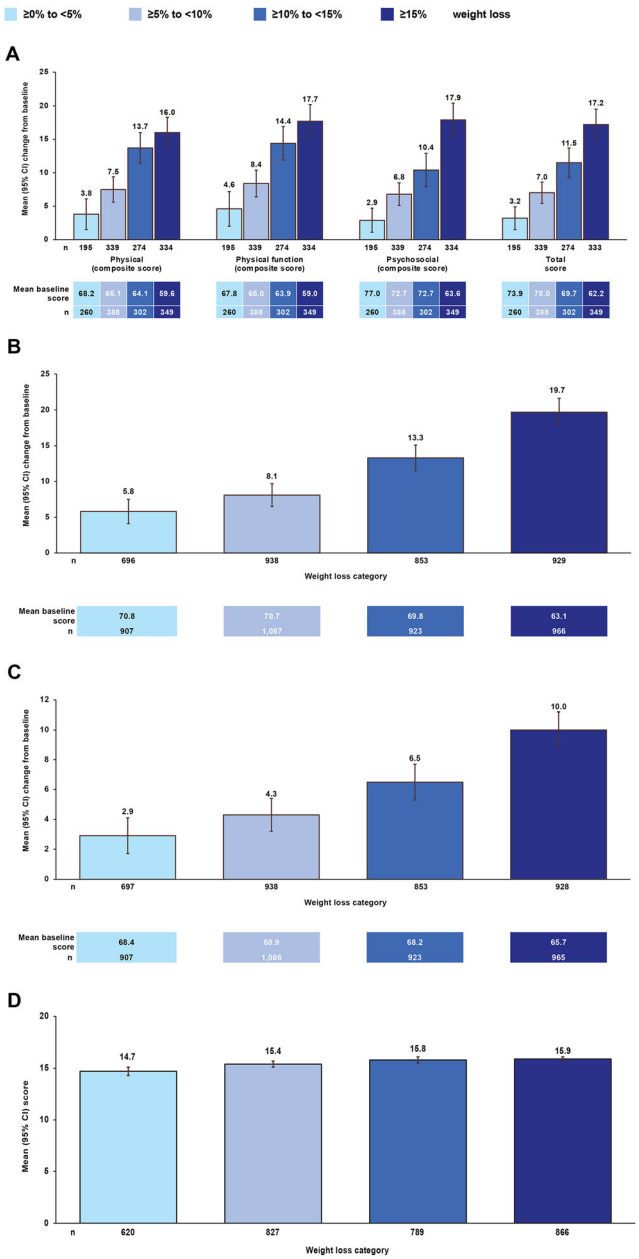


Fig. 3 PROs for adults with type 2 diabetes treated with tirzepatide (any dose*) achieving 0 ≤ to < 5%, 5 ≤ to < 10%, 10 ≤ to < 15% or ≥ 15% weight loss at endpoint in SURPASS-1 to -5. **A** Changes from baseline in IWQOL-Lite-CT composite and total scores at endpoint. **B** Changes from baseline in IW-SP total score† at endpoint. **C** Changes from baseline in APPADL total score† at endpoint. **D** Endpoint DTSQc total treatment satisfaction scores. **E** Endpoint DTSQc hypoglycaemia and hyperglycaemia scores. **F** Changes from baseline in EQ-5D-5L index score at endpoint. **G** Changes from baseline in EQ VAS at endpoint. *Any dose = 5, 10 or 15 mg administered by subcutaneous injection once weekly. † Transformed IW-SP and APPADL scores presented above have been linearly transformed from raw scores to a scale of 0–100. IWQOL-Lite-CT was only measured in SURPASS-2. DTSQc was only measured in SURPASS-2 to -5. All other PROs were measured in all five SURPASS studies. *APPADL* Ability to Perform Physical Activities of Daily Living, *CI* confidence interval, *DTSQc* Diabetes Treatment Satisfaction Questionnaire change, *IWQOL-Lite-CT* Impact of Weight on Quality of Life-Lite Clinical Trials Version, *IW-SP* Impact of Weight on Self-Perception, *PRO* patient-reported outcome, *VAS* visual analogue scale

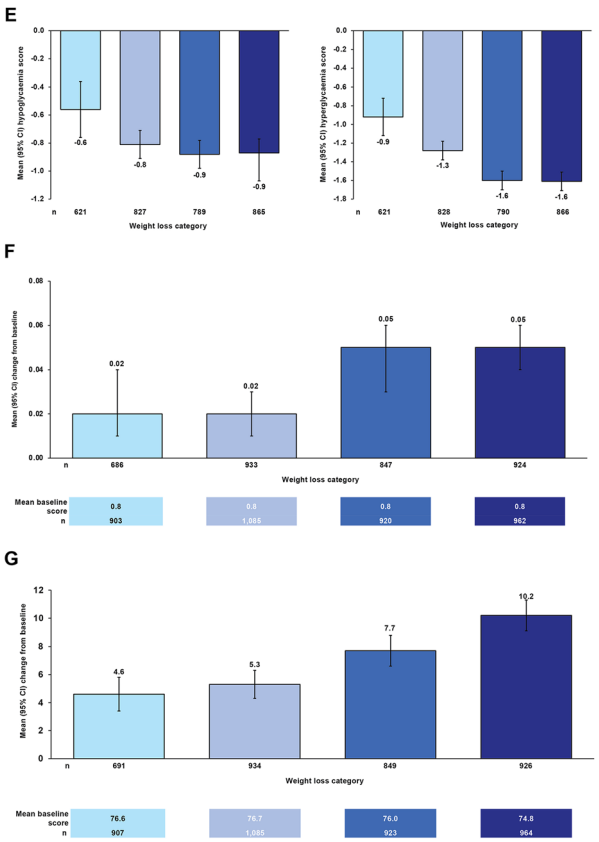


Fig. 3 continued

previously been seen with GLM, results in improved health-related QoL for these patients.

Measuring the QoL impact of weight loss is important for people with T2D as many also have obesity, which is well known to negatively impact health-related QoL [27]. In addition, the detrimental effect of increasing BMI on the health-related QoL of people with T2D has been reported in the literature. For example, in the European PANORAMA study, which measured health-related QoL in 5813 people with T2D using the Audit of Diabetes-Dependent Quality of Life, multivariable analysis indicated that having a lower BMI was significantly associated with better health-related QoL and a better health state on the EQ VAS ($p < 0.001$) [28]. Weight loss was associated with improved PROs, including physical functioning, in this analysis of participants treated with tirzepatide in SURPASS-1 to -5, with the greatest improvement observed in participants achieving higher weight loss percentages. The ADA recommends that a medication's effect on weight should be considered when choosing GLMs for people with T2D and overweight or obesity as these individuals 'may benefit from modest or larger magnitudes of weight loss' [2]. The T2D management guidelines highlight that 'larger sustained weight losses (> 10%) usually confer greater benefits, including disease-modifying effects and possible remission of T2D, and may improve long-term cardiovascular outcomes and mortality' [2]. These recommendations reflect the available evidence from secondary analyses of the Look AHEAD (Action for Health in Diabetes) trial and other large cardiovascular outcome studies, which have also documented additional weight loss benefits in people with T2D who achieved > 10% weight loss, including improved mobility, physical and sexual function and health-related QoL [29, 30].

Our study is an important addition to the literature on this topic, as the opportunity to evaluate the association between QoL and the high levels of weight loss achieved with tirzepatide treatment (e.g. > 10% weight loss) in a T2D population using relevant PRO measures has not previously arisen. Along with glycaemic improvement, tirzepatide treatment has demonstrated substantial weight reduction effects in the SURPASS-1 to -5 Phase 3 clinical trials [9–13]. In the SURPASS-2 study, reductions in body weight were greater with tirzepatide 5, 10 and 15 mg than with semaglutide 1 mg (the approved dosage at the time of the study; least squares mean estimated treatment difference − 1.9 kg, − 3.6 kg and − 5.5 kg, respectively; $p < 0.001$ for all comparisons) [10]. The results of our study support the theory that greater weight loss results in better QoL in this patient population, based on the SURPASS-1 to -5 studies, which provide a rich source of data that has not previously been available for GLMs.

The results of our three-way analyses of PROs in study participants achieving each combination of HbA1c (%) target and weight loss from baseline suggest that achievement of lower HbA1c (%) targets in combination with greater weight loss is generally associated with enhanced QoL. Perhaps as expected, PROs derived from measures evaluating different

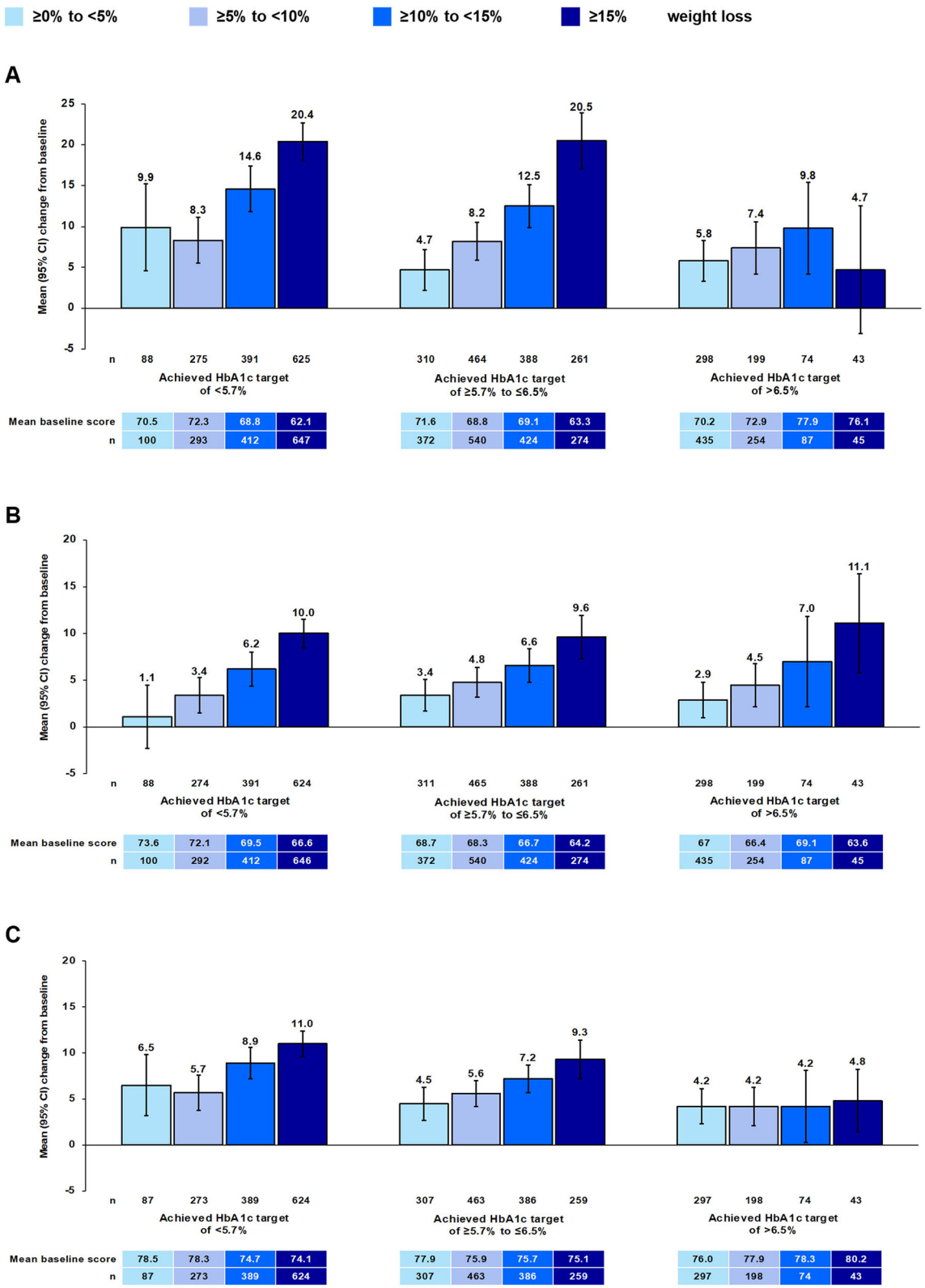

≥0% to <5%
≥5% to <10%
≥10% to <15%
≥15% weight loss
A
Mean (95% CI) change from baseline
25
20
15
10
5
0
-5
9.9
8.3
14.6
20.4
4.7
8.2
12.5
20.5
5.8
7.4
9.8
4.7
n 88 275 391 625
310 464 388 261
298 199 74 43
Achieved HbA1c target of <5.7%
Achieved HbA1c target of ≥5.7% to ≤6.5%
Achieved HbA1c target of >6.5%
Mean baseline score 70.5 72.3 68.8 62.1
71.6 68.8 69.1 63.3
70.2 72.9 77.9 76.1
n 100 293 412 647
372 540 424 274
435 254 87 45
B
Mean (95% CI) change from baseline
20
15
10
5
0
-5
1.1
3.4
6.2
10.0
3.4
4.8
6.6
9.6
2.9
4.5
7.0
11.1
n 88 274 391 624
311 465 388 261
298 199 74 43
Achieved HbA1c target of <5.7%
Achieved HbA1c target of ≥5.7% to ≤6.5%
Achieved HbA1c target of >6.5%
Mean baseline score 73.6 72.1 69.5 66.6
68.7 68.3 66.7 64.2
67 66.4 69.1 63.6
n 100 292 412 646
372 540 424 274
435 254 87 45
C
Mean (95% CI) change from baseline
20
15
10
5
0
-5
6.5
5.7
8.9
11.0
4.5
5.6
7.2
9.3
4.2
4.2
4.2
4.8
n 87 273 389 624
307 463 386 259
297 198 74 43
Achieved HbA1c target of <5.7%
Achieved HbA1c target of ≥5.7% to ≤6.5%
Achieved HbA1c target of >6.5%
Mean baseline score 78.5 78.3 74.7 74.1
77.9 75.9 75.7 75.1
76.0 77.9 78.3 80.2
n 87 273 389 624
307 463 386 259
297 198 74 43

Fig. 4 Patient-reported outcomes for adults with type 2 diabetes treated with tirzepatide (any dose*) achieving HbA1c (%) targets of $< 5.7\%$, $\geq 5.7\%$ to $\leq 6.5\%$ or $> 6.5\%$ and ≥ 0 to $< 5\%$, ≥ 5 to $< 10\%$, ≥ 10 to $< 15\%$ or $\geq 15\%$ weight loss at endpoint in SURPASS-1 to -5. **A** Changes from baseline in IW-SP total score† at endpoint. **B** Changes from baseline in APPADL total score† at endpoint. **C** Changes from baseline in EQ VAS at endpoint. *Any dose = 5, 10 or 15 mg administered by subcutaneous injection once weekly. †Transformed IW-SP and APPADL scores presented above have been linearly transformed from raw scores to a scale of 0–100. IW-SP, APPADL and EQ VAS were measured in all five SURPASS studies. *APPADL* Ability to Perform Physical Activities of Daily Living, *CI* confidence interval, *HbA1c* glycated haemoglobin, *IW-SP* Impact of Weight on Self-Perception, *VAS* visual analogue scale

concepts associated with weight-related QoL appeared to be more affected by greater weight loss in our analyses.

Limitations

Limitations of these analyses include the administration of PRO measures in a clinical trial setting. As a result, reported PROs may not reflect those that may be observed in a real-world setting, where people with T2D may have less contact with/support from HCPs. Furthermore, the open-label study design of SURPASS-2, -3 and -4 may have influenced participants to over- or underestimate their treatment assessments based on their beliefs regarding their assigned treatment. Although PRO changes were measured at the same time as changes in HbA1c (%) and weight in each trial, not all measurements were taken at the same time point across trials (i.e. Week 40 or 52) and weight loss had not plateaued in the SURPASS-1 to -5 Phase 3 clinical trials; therefore, continued weight reduction may have occurred, and PROs could have improved further with a longer follow-up period. Furthermore, the health-related QoL outcomes associated with tirzepatide in this analysis were limited to the PRO instruments used in the clinical trials. For example, additional factors influencing health-related QoL, such as satiety, vitality, lack of worry and overall mental health, were not captured. Finally, the sample sizes in some combination HbA1c (%) target achieved/weight loss from baseline categories in the three-way analyses were low; therefore, results should be interpreted with caution.

CONCLUSION

Achievement of lower HbA1c (%) targets or higher percentage of body weight losses were each associated with greater improvements in health-related QoL among adults receiving any dose of tirzepatide in SURPASS-1 to -5 than achievement of higher HbA1c (%) targets or lower percentage of body weight losses, respectively. Furthermore, achievement of lower HbA1c (%) targets in combination with greater weight loss was generally associated with the highest QoL ratings. The findings of this analysis therefore demonstrate that HbA1c (%) targets and significant percentage body weight reduction thresholds need to be achieved to help people with T2D substantially increase their overall health-related QoL. Treatment with tirzepatide may allow a high proportion of people with T2D to achieve these targets and thereby have improved QoL.

ACKNOWLEDGEMENTS

Medical Writing, Editorial and Other Assistance. The authors would like to thank the programming team involved in the delivery of the analyses and Maria Yu (Eli Lilly and Company) for statistical input. The authors would also like to acknowledge Caroline Spencer (Rx Communications, Mold, UK) for medical writing assistance with the preparation of this manuscript, funded by Eli Lilly and Company.

Author Contributions. Kristina S. Boye has made substantial contributions to the conception and design of the work, the interpretation of the data for the work and critical revision of the manuscript. Hélène Sapin has made substantial contributions to the analysis and

interpretation of the data for the work and critical revision of the manuscript for important intellectual content. Wenxiu Dong has made substantial contributions to the analysis and interpretation of the data for the work and critical revision of the manuscript for important intellectual content. Suzanne Williamson has made substantial contributions to the interpretation of the data for the work, the drafting and critical revision of the manuscript for important intellectual content. Clare J. Lee has made substantial contributions to the analysis and interpretation of the data for the work and critical revision of the manuscript for important intellectual content. Vivian Thuyanh Thieu has made substantial contributions to the conception and acquisition of data for the work, the analysis and interpretation of data for the work, the drafting and critical revision of the manuscript for important intellectual content.

Funding. This study as well as the journal's Rapid Service fee was sponsored and funded by Eli Lilly and Company.

Data Availability. Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and the European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at: http://www.vivli.org.

Declarations

Conflict of interest. Kristina S Boye, Hélène Sapin, Clare J. Lee and Vivian Thuyanh Thieu are full-time employees and minor stockholders of Eli Lilly and Company. Wenxiu Dong and Suzanne Williamson work as consultants for Eli Lilly and Company.

Ethical approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Study protocols were approved by local ethical review boards, and all participants provided written informed consent. All studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

REFERENCES

1. American Diabetes Association (ADA). 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes—2023. Diabetes Care. 2023;46(Suppl 1):S140–57.

2. American Diabetes Association (ADA). 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: standards of care in diabetes—2023. Diabetes Care. 2023;46(Suppl 1):S128–39.

3. Wing RR, Lang W, Wadden TA, Look AHEAD Research Group, 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(7):1481–6.

4. Ryan DH, Yockey SR. Weight loss and improvement in comorbidity: differences at 5%, 10%, 15% and over. Curr Obes Rep. 2017;6(2):187–94.

5. Inzucchi SE, Bergenstal RM, Buse JB, American Diabetes Associations (ADA) and European Association for the Study of Diabetes (EASD), 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(6):1364–79.

6. United States Food and Drug Administration. Prescribing information: MOUNJARO (tirzepatide) injection, for subcutaneous use; 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215866s000lbl.pdf. Accessed 19 May 2023.

7. European Medicines Agency. Mounjaro (tirzepatide) 2.5, 5, 7.5, 10, 12.5, 15 mg solution for injection in pre-filled pen Summary of Product Characteristics; 2023. https://www.ema.europa.eu/en/documents/product-information/mounjaro-epar-product-information_en.pdf. Accessed 19 May 2023.

8. American Diabetes Association (ADA) [online]. Diabetes overview. Understanding A1c; ©1995–2023. https://diabetes.org/diabetes/a1c. Accessed 19 May 2023.

9. Rosenstock J, Wysham C, Frías JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet. 2021;398(10295):143–55.

10. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021;385(6):503–15.

11. Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. Lancet. 2021;398(10300):583–9.

12. Del Prato S, Kahn SE, Pavo I, SURPASS-4 Investigators, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet. 2021;398(10313):1811–24.

13. Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. JAMA. 2022;327(6):534–45.

14. Institute for Clinical and Economic Review (ICER). Tirzepatide for type 2 diabetes: final policy recommendations. February 15, 2022. https://icer.org/wp-content/uploads/2022/02/ICER_Type2Diabetes_PolicyRecommendations_02152022.pdf. Accessed 19 May 2023.

15. American Diabetes Association (ADA). 5. Facilitating positive health behaviors and well-being to improve health outcomes: standards of care in diabetes—2023. Diabetes Care. 2023;46(Suppl 1):S68–96.

16. Boye KS, Thieu VT, Sapin H, et al. Patient-reported outcome results in patients with T2D on tirzepatide SURPASS clinical trial programme. Diabetes Ther. 2023. https://doi.org/10.1007/s13300-023-01451-z.

17. Pederen SD, Giorgino F, Umpierrez G, et al. Relationship between body weight change and glycemic control with tirzepatide treatment in people with type 2 diabetes in the SURPASS clinical trial program. Diabetes Obes Metab. 2023. https://doi.org/10.1111/dom15140.

18. World Medical Association. Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA. 1997;277(11):925–6.

19. EuroQoL Research Foundation. EQ-5D-5L user guide, version 3.0, September 2019. https://euroqol.org/publications/user-guides. Accessed 19 May 2023.

20. Bradley C, Lewis KS. Measures of psychological well-being and treatment satisfaction developed from the responses of people with tablet-treated diabetes. Diabetes Med. 1990;7(5):445–51.

21. Kolotkin RL, Williams VSL, Ervin CM, et al. Validation of a new measure of quality of life in obesity trials: impact of weight on quality of life-lite clinical trials version. Clin Obes. 2019;9(3): e12310.

22. Hayes RP, DeLozier AM. Reliability, validity, and responsiveness of the Impact of Weight on Self-Perceptions Questionnaire (IW-SP) in individuals with type 2 diabetes and obesity. Diabetes Technol Ther. 2015;17(3):210–4.

23. Hayes RP, Nelson DR, Meldeahl ML, Curtis NH. 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(7):705–12.

24. 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(12):1118–25.

25. American Diabetes Association (ADA). 6 Glycemic targets: standards of care in diabetes—2023. Diabetes Care. 2023;46(Suppl 1):S97–110.

26. United States Food and Drug Administration. 2022. Prescribing information: INVOKANA (canaglifozin) tablets, for oral use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204042s011lbl.pdf. Accessed 19 May 2023.

27. Kolotkin RL, Andersen JR. A systematic review of reviews: exploring the relationship between obesity, weight loss and health-related quality of life. Clin Obes. 2017;7(5):273–89.

28. Bradley C, Eschwège E, de Pablos-Velasco P, et al. Predictors of quality of life and other patient-reported outcomes in the PANORAMA multinational study of people with type 2 diabetes. Diabetes Care. 2018;41(2):267–76.

29. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136(6): e137-61.

30. Look AHEAD Research Group, Gregg E, Jakicic JM, Blackburn G, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol. 2016;4(11):913–21.

31. Kolotkin RL. IWQOL-Lite Clinical Trials Version©; 2021. https://www.qualityoflifeconsulting.com/iwqol-lite-clinical-trials.html. Accessed 19 May 2023.

32. Gelhorn H, Maher S, Sapin H, et al. Estimating meaningful change for the Impact of Weight on Self-Perception (IW-SP) questionnaire among people with type 2 diabetes. Qual Life Res. 2023. https://doi.org/10.1007/s11136-023-03476-0.

33. Bradley C. The Diabetes Treatment Satisfaction Questionnaire (DTSQ). Change version for use alongside status version provides appropriate solution where ceiling effects occur. Diabetes Care. 1999;22(3):530–2.

34. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708–15.

35. McClure NS, Al Sayah F, Ohinmaa A, Johnson JA. Minimally important differences of the EQ-5D-5L index score in adults with type 2 diabetes. Value Health. 2018;21(9):1090–7.