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Relationship between body weight change and glycaemic control with tirzepatide treatment in people with type 2 diabetes: A post hoc assessment of the SURPASS clinical trial programme

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Abstract

Aim: To assess the relationship between HbA1c and body weight reductions with tirzepatide treatment (5, 10 or 15 mg).

Materials and Methods: HbA1c and body weight data at 40 weeks (SURPASS-1, -2 and -5) and 52 weeks (SURPASS-3 and -4) were analysed by trial.

Results: Across the SURPASS clinical trials, HbA1c reductions from baseline were observed in 96%-99%, 98%-99% and 94%-99% of participants treated with tirzepatide 5, 10 and 15 mg, respectively. Moreover, 87%-94%, 88%-95% and 88%-97% of participants, respectively, experienced weight loss associated with HbA1c reductions. Statistically significant associations (correlation coefficients ranging from 0.1438 to 0.3130 across studies; $P \leq .038$) between HbA1c and body weight changes were observed with tirzepatide in SURPASS-2, -3, -4 (all doses) and -5 (tirzepatide 5 mg only).

Conclusions: In this post hoc analysis, consistent reductions in both HbA1c and body weight were observed in most participants treated with tirzepatide at doses of 5, 10 or 15 mg. A statistically significant but modest association between HbA1c and body weight change was observed in SURPASS-2, SURPASS-3 and SURPASS-4, suggesting that both weight-independent and weight-dependent mechanisms are responsible for the tirzepatide-induced improvement in glycaemic control.

KEYWORDS
body weight, glycaemic control, tirzepatide, type 2 diabetes

1 | INTRODUCTION

Tirzepatide, a novel glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, was recently approved for the treatment of type 2 diabetes (T2D) in the United States, Europe and several other jurisdictions.[1,2] Tirzepatide is also currently under investigation for chronic weight management, heart failure with preserved

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ejection fraction, non-alcoholic steatohepatitis and obstructive sleep apnoea.

In the phase 3 SURPASS clinical trial programme, treatment with once-weekly tirzepatide at all doses tested (5, 10 and 15 mg) resulted in robust improvements in glycaemic control across the continuum of T2D, including tirzepatide as monotherapy, in combination with 1-3 oral glucose-lowering medications, or as add-on to basal insulin. In participants who were on treatment without the use of rescue therapy, tirzepatide treatment significantly reduced HbA1c −1.87% to −2.59%) compared with placebo or active comparators (i.e. semaglutide 1 mg, insulin degludec, insulin glargine).[3–7] Furthermore, 81%-97% of participants achieved an HbA1c of less than 7.0% and 23%-62% achieved an HbA1c of less than 5.7%.[3–7] In a mechanism-of-action study in people with T2D, tirzepatide was shown to improve glycaemic control by enhancing pancreatic beta-cell function, improving insulin sensitivity and suppressing glucagon secretion,[8] as well as reducing food intake.[9]

The robust glycaemic control observed with tirzepatide treatment in the phase 3 global registration trials (SURPASS-1 through SURPASS-5) was associated with clinically meaningful body weight reductions.[3–7] Study participants treated with tirzepatide lost on average 6-13 kg (7%-14%) of body weight. Furthermore, among various clinical trials with different study populations, background therapies and study designs, tirzepatide treatment showed greater reductions in HbA1c and body weight compared with selective GLP-1 receptor agonists dulaglutide 0.75 and 1.5 mg[10,11] and semaglutide 1 mg,[7,8] with similar safety and tolerability profiles. A recently published indirect treatment comparison reported significantly greater HbA1c and weight reductions with tirzepatide at the 10 and 15 mg doses and similar reductions with the 5 mg dose compared with semaglutide 2 mg.[12] However, head-to-head trials designed to compare the efficacy and safety of tirzepatide with higher dose GLP-1 receptor agonists are still needed.

Numerous studies have shown that, irrespective of treatment modality, weight loss is associated with improvement in glycaemic control in people with T2D.[13–15] Given that improvements in glycaemic control may be linked to both weight-independent and weight-dependent mechanisms, it is of interest to understand how changes in glycaemia and weight seen with tirzepatide are related.

This post hoc analysis assessed the relationship between HbA1c and body weight reductions with tirzepatide treatment (5, 10 or 15 mg) across the SURPASS-1 through SURPASS-5 clinical trials. The proportions of participants with different treatment responses (HbA1c decrease or increase with weight loss or weight gain) were assessed, and the association between weight loss and HbA1c changes in each trial was evaluated. We aimed to evaluate the relationship between weight loss and glucose lowering observed with tirzepatide, and contrast results with those seen with GLP-1 receptor agonists. We deemed this analysis of interest because tirzepatide treatment impacted body weight and HbA1c to a greater extent compared with GLP-1 receptor agonists.

2 | METHODS

2.1 | Design of the SURPASS clinical trial programme

The study designs, background medications, full inclusion and exclusion criteria and primary results of the SURPASS-1 through SURPASS-5 clinical trials have been previously reported.[3–7] Briefly, the phase 3 SURPASS clinical trials were randomized controlled clinical studies, ranging from 40 to 104 weeks in duration, with a total of 6263 participants. The SURPASS clinical trials were designed to evaluate the safety and efficacy of tirzepatide (5, 10 or 15 mg) in adults with T2D. The primary efficacy measure of HbA1c reduction from baseline at the primary endpoints of 40 or 52 weeks, depending on the individual trial, was superiority of tirzepatide compared with placebo or non-inferiority of tirzepatide compared with active comparators (semaglutide 1 mg, insulin degludec or insulin glargine). If non-inferiority of tirzepatide compared with active comparator was met, then subsequent testing for superiority was undertaken. The SURPASS clinical trials did not include any specific recommendation regarding diet and exercise beyond the usual practice at each study centre. Concomitant pharmacotherapy that promoted weight loss was not allowed.

The SURPASS clinical trials assessed in this analysis were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All participants provided signed informed consent and protocols were approved by local ethical review boards.

2.2 | Statistical analyses

The SURPASS-1 to SURPASS-5 trials were analysed separately using data at the primary endpoints of 40 or 52 weeks, because of differences in design and background therapy. This post hoc analysis included randomized and treated study participants with available body weight and HbA1c data at the primary endpoints of 40 or 52 weeks, excluding data after rescue or discontinuation of study drug. For each study and treatment arm, scatterplots of changes from baseline in HbA1c versus changes from baseline in body weight at the primary endpoints were developed. Pearson correlation coefficients were determined for HbA1c change versus body weight change and percentage body weight change, respectively. Data were also explored by categorical response: lower left (LL) quadrant, both decrease in HbA1c and body weight (change from baseline < 0 for both); upper left (UL) quadrant, decrease in HbA1c, no change/increase in body weight (change from baseline ≥ 0); upper right (UR) quadrant, both no change/increase in HbA1c and body weight; and lower right (LR) quadrant, no change/increase in HbA1c and decrease in body weight. The relationship between body weight and HbA1c changes at primary endpoints were further investigated through analysing HbA1c changes according to the following categories of percentage body weight changes: no change or weight gain; weight loss of more than 0% to less than 5%; weight loss of 5% or

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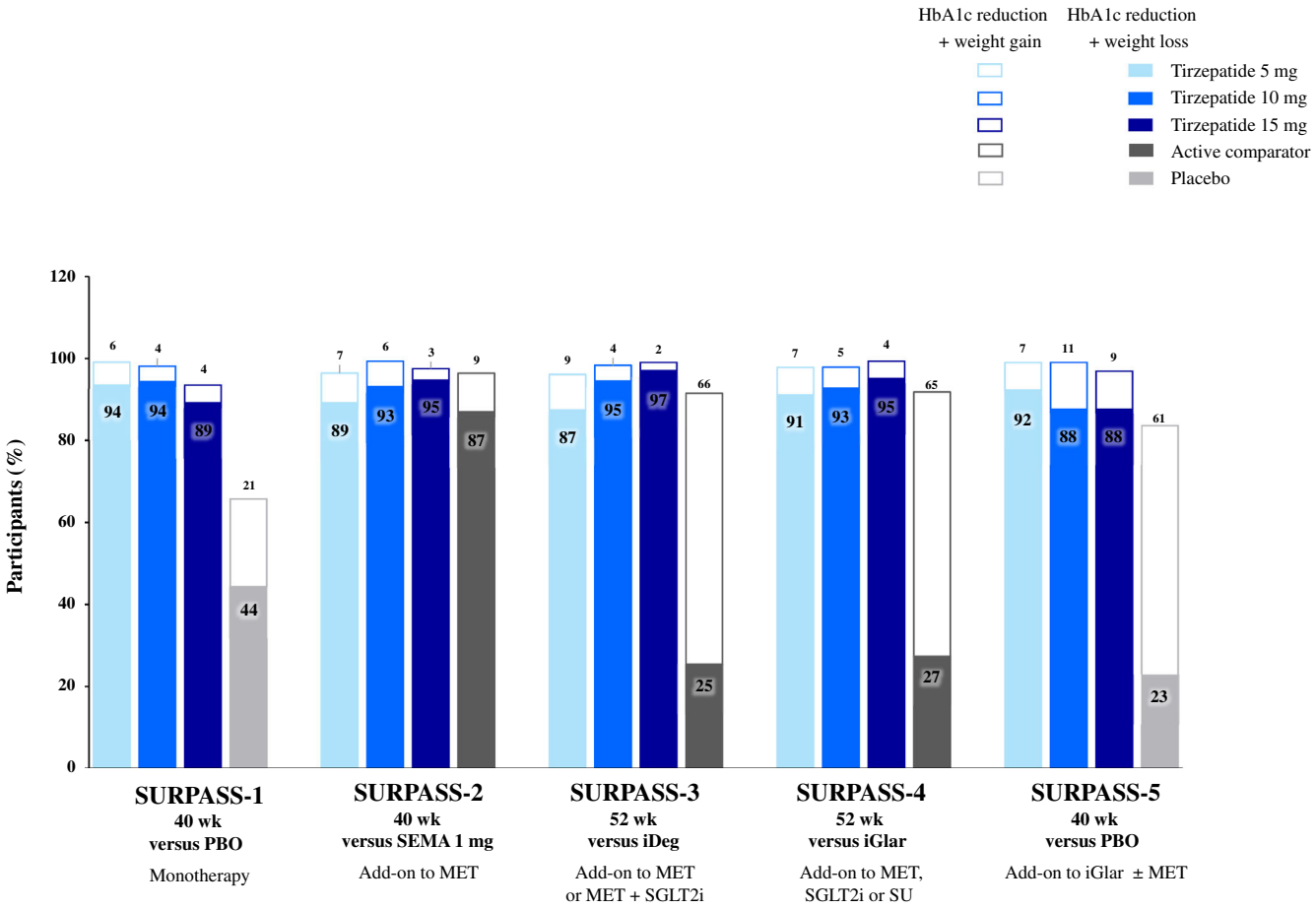

FIGURE 1 The proportion of participants with HbA1c reduction and either weight reduction or no weight change/weight gain at the primary endpoint. Data are presented as the proportion of participants with HbA1c reduction + weight loss (solid bars) and HbA1c reduction or no weight change or weight gain (open bars). Analysed populations include randomized and treated study participants with available body weight and HbA1c data at the primary endpoint of week 40 (SURPASS-1, SURPASS-2 and SURPASS-5) or week 52 (SURPASS-3 and SURPASS-4), excluding data after rescue or discontinuation of study drug. Change from baseline in HbA1c reductions and weight loss or gain was defined as any change at the primary endpoint. The sum of percentages in each bar do not necessarily equal 100 as they only represent two out of four quadrants. iDeg, insulin degludec; iGlar, insulin glargine; MET, metformin; PBO, placebo; SEMA, semaglutide; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea

higher to less than 10%; weight loss of 10% or higher to less than 15%; and weight loss of 15% or higher.

Continuous variables were summarized as means and standard deviations, and categorical variables as counts and proportions. Missing values were not imputed.

All analyses presented are exploratory in nature, and *P* less than .05 was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

3 | RESULTS

A total of 6263 participants with T2D were enrolled in the SURPASS-1 through SURPASS-5 clinical trials (tirzepatide 5 mg, $N = 1394$; tirzepatide 10 mg, $N = 1397$; tirzepatide 15 mg, $N = 1408$; semaglutide 1 mg, $N = 469$; insulin degludec, $N = 360$; insulin glargine, $N = 1000$; placebo, $N = 235$). This post hoc analysis included 5378 participants (85.9%) across all studies. The baseline demographics and clinical characteristics within each trial were similar across treatment arms (Table **S1**).

3.1 | HbA1c and body weight at the primary endpoint

Tirzepatide at all doses reduced HbA1c across the diabetes treatment continuum, with observed mean reductions ranging from 1.90% to 2.65% (Table S2).[3–7] Furthermore, dose-dependent weight changes varied based on the background therapy, with mean reductions ranging from 6.11 kg (6.6%) with tirzepatide 5 mg from SURPASS-5 to 13.10 kg (13.8%) with tirzepatide 15 mg from SURPASS-3 (Table S2).

Across the SURPASS clinical trials, HbA1c reductions from baseline were observed in 96%-99%, 98%-99% and 94%-99% of participants treated with tirzepatide 5, 10 and 15 mg, respectively (Figure 1). Body weight reductions from baseline were observed in

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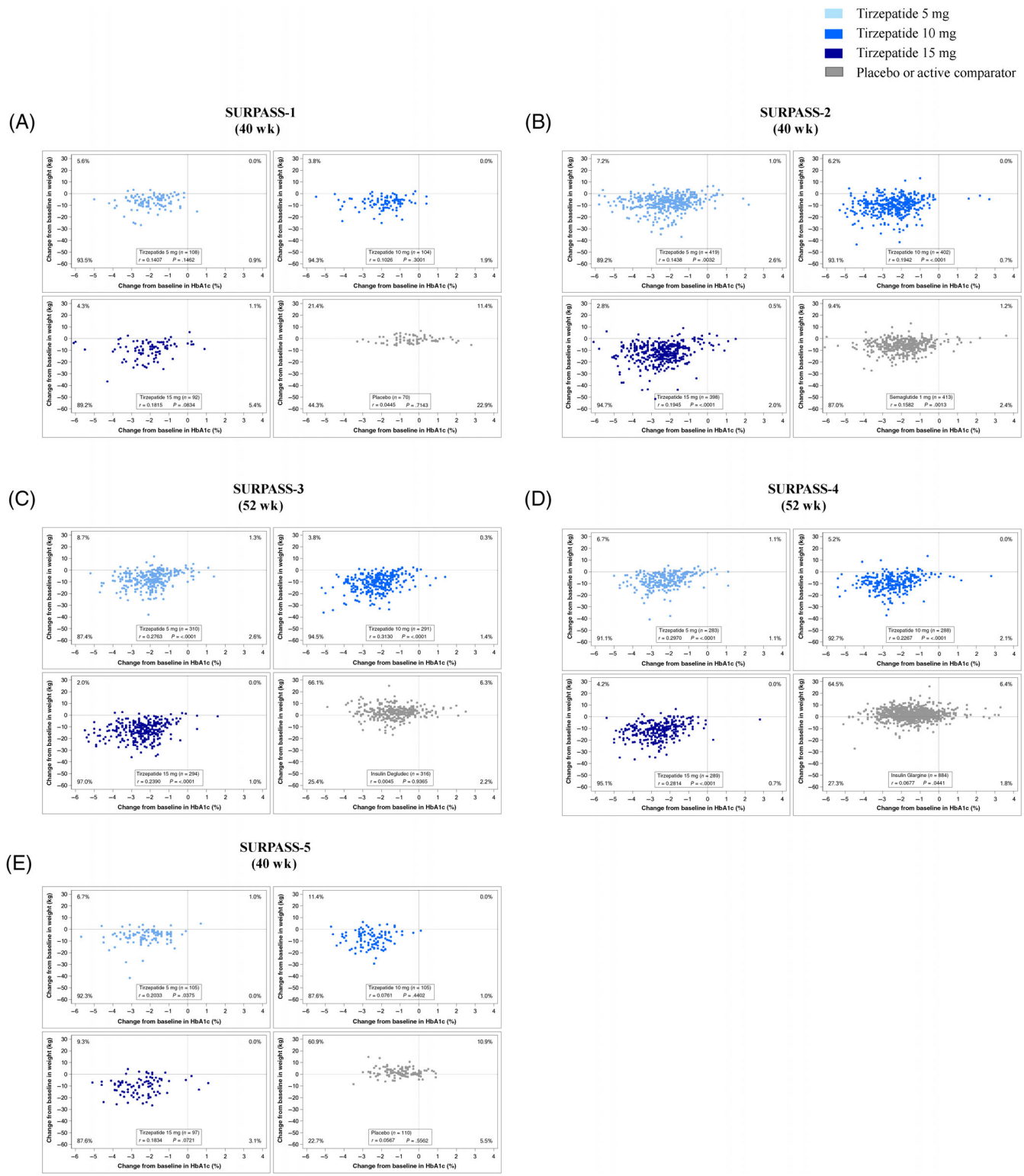

FIGURE 2 Correlation coefficients between changes from baseline in HbA1c and body weight. Data are observed values for change from baseline in HbA1c (%) and change from baseline in weight (%) to the primary endpoint of week 40 (A: SURPASS-1, B: SURPASS-2 and E: SURPASS-5) or week 52 (C: SURPASS-3 and D: SURPASS-4). Analysed populations include randomized and treated study participants with available body weight and HbA1c data at the primary endpoint of week 40 or week 52, excluding data after rescue or discontinuation of study drug. Where percentages across quadrants did not sum up to 100% initially because of rounding, the percentage given for the lower left (LL) quadrant was adapted accordingly

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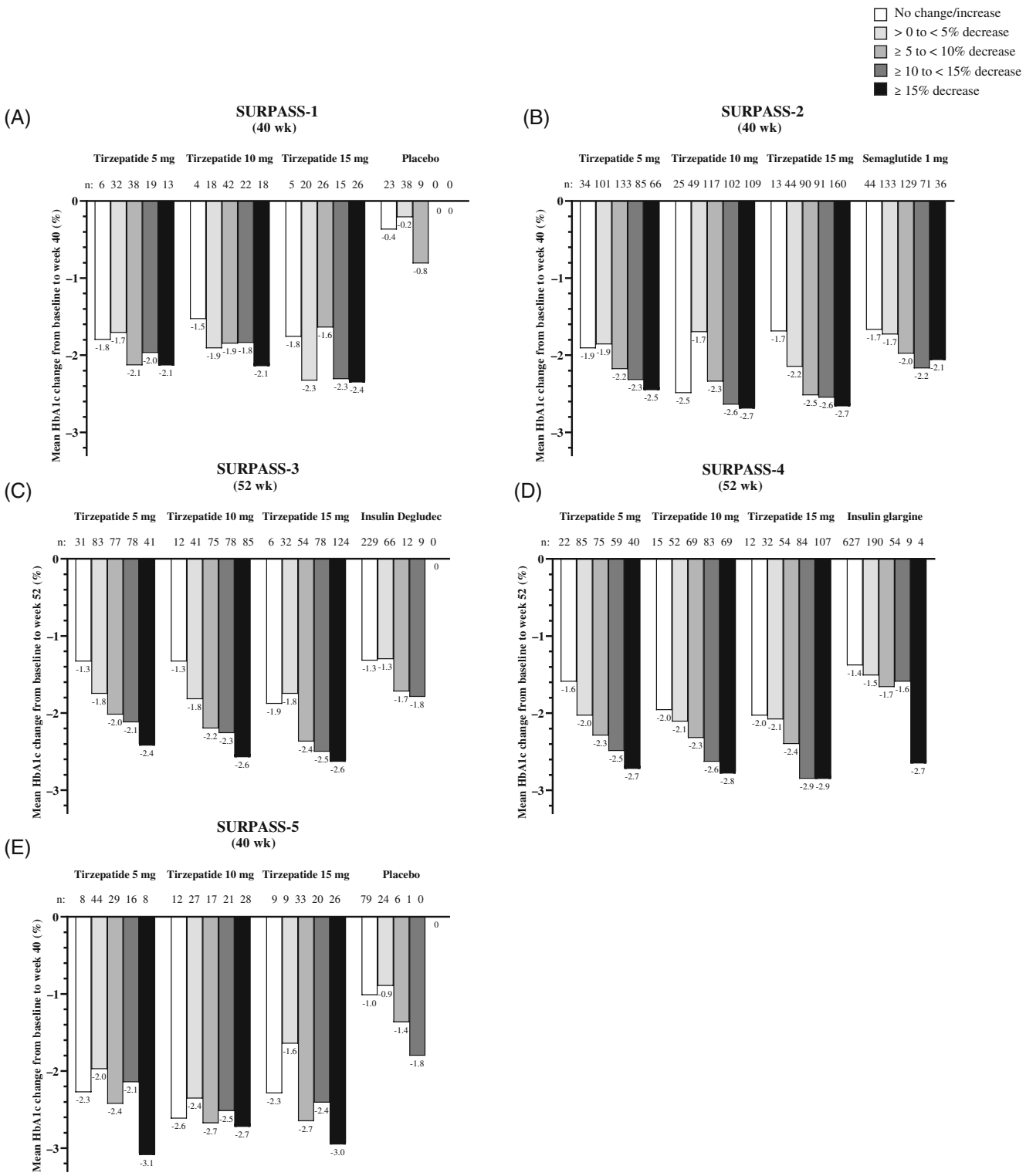

FIGURE 3 Mean HbA1c change from baseline categorized by percentage body weight change from baseline. Data are mean HbA1c values at the primary endpoint of week 40 (A: SURPASS-1, B: SURPASS-2 and E: SURPASS-5) or week 52 (C: SURPASS-3 and D: SURPASS-4). Analysed populations include randomized and treated study participants with available body weight and HbA1c data at the primary endpoint of week 40 or week 52, excluding data after rescue or discontinuation of study drug

87%-94%, 88%-95% and 88%-97% of participants treated with tirzepatide 5, 10 and 15 mg, respectively. Furthermore, the vast majority of participants (87%-97%) receiving any dose of tirzepatide experienced both weight loss and HbA1c reduction (Figure 1). Associations between HbA1c and body weight changes were observed with tirzepatide in SURPASS-2, SURPASS-3, SURPASS-4 (all doses) and

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SURPASS-5 (tirzepatide 5 mg only) with statistically significant correlation coefficients ranging from 0.1438 to 0.3130 across studies ($P \leq .038$ for all tirzepatide doses; Figure 2 and Table S3). Correlation coefficient results were consistent between HbA1c and both percentage and absolute weight changes, and across these SURPASS trials.

Mean changes in HbA1c and body weight for participants who displayed HbA1c reductions and body weight loss and for participants who displayed HbA1c reduction and body weight gain are presented in Table S4.

At the primary endpoint of 40 or 52 weeks, categorical analyses generally showed greater HbA1c reduction with more weight loss for each tirzepatide dose (Figure 3). These observations were not seen in the SURPASS-1 monotherapy study or in SURPASS-5.

4 | DISCUSSION

There is an increasing recognition that excess body weight, denoting excessive and dysfunctional adipose tissue,[16] is an important contributor in the development of T2D. Weight management has been recognized as a critical element of treatment of people with T2D, and it is considered to be as important as the management of elevated blood glucose levels.[17] Even a modest amount of weight loss can improve glycaemia and improve other metabolic abnormalities.[13,14] Moreover, weight loss of a higher magnitude can lower the risk of complications and have further disease-modifying effects.[13,17] Lifestyle modification is recommended as the first-line approach to weight loss; however, lifestyle modification alone is insufficient for achieving and maintaining long-term weight loss in many patients,[13] and several conventional glucose-lowering medications, while effective in improving glycaemic control, are weight-neutral or even promote weight gain.[13,18]

Tirzepatide, a once-weekly GIP and GLP-1 receptor agonist, showed robust glycaemic and weight efficacy in the SURPASS clinical trial programme, with a similar safety profile to that of the GLP-1 receptor agonist class. The most frequent adverse events were gastrointestinal in nature (i.e. nausea, vomiting, diarrhoea), mild to moderate in intensity, and mostly reported during dose escalation.[3–7] Weight loss occurred irrespective of the presence or absence of gastrointestinal adverse events, and weight loss did not reach a plateau at 1 year.[19] Although treatment with tirzepatide improves multiple surrogate markers of cardiovascular risk to a greater extent than GLP-1 receptor agonists, including blood glucose, blood pressure and serum lipids, it remains to be established what impact tirzepatide treatment might have on cardiovascular disease. This is currently being studied in the ongoing head-to-head cardiovascular outcome trial SURPASS-CVOT with the selective GLP-1 receptor agonist, dulaglutide.

This post hoc analysis elucidated the relationship between body weight changes and improvements in glycaemic control in patients treated with tirzepatide. Across the five SURPASS trials, significant HbA1c and body weight reductions were observed in the vast majority of patients treated with all doses of tirzepatide (5, 10 and 15 mg). Furthermore, treatment with tirzepatide showed a statistically significant, albeit modest (correlation coefficients 0.1438-0.3130), association between HbA1c reduction and the effect on body weight.

Similar analyses performed with data from GLP-1 receptor agonists dulaglutide, liraglutide, exenatide twice daily and semaglutide have shown that there tended to be greater HbA1c reduction with greater weight loss. Modest correlation coefficients for HbA1c and weight loss were observed for liraglutide (0.248) and for exenatide twice daily (0.202), while results for dulaglutide and semaglutide were not consistent (−0.223 to 0.267 for dulaglutide and −0.04 to 0.32 for semaglutide).[20–23] The association between HbA1c reduction and the effect on body weight was of comparably modest magnitude for tirzepatide, despite the greater glycaemic efficacy and weight-lowering effect of this dual incretin receptor agonist than with semaglutide 1 mg and dulaglutide 1.5 mg.[7,8,10] The results suggest an association between weight loss and glycaemic improvement. If true, several mechanisms may be involved in the weight loss-mediated lowering of glycaemia. The impact of weight loss on insulin sensitivity has been well established, even although results of preclinical and clinical studies indicate that improvement of insulin sensitivity with tirzepatide is not entirely weight dependent.[11,24,25] Other putative mechanisms include improvements in pro-inflammatory signalling by dysfunctional adipose tissue and lowering of the lipotoxicity effect on beta cells to improve secretory function.[16,26] Of note, improvement in insulin sensitivity with tirzepatide has been shown to be greater per unit of weight lost than with the GLP-1 receptor agonist semaglutide.[8]

Associations between HbA1c and body weight were not observed in SURPASS-1 at all tirzepatide doses or in SURPASS-5 at the 10 and 15 mg doses. Notably, these studies enrolled a smaller population than the others did, which might have increased variability. The two studies also had some distinct population features. SURPASS-1 was unique because it involved people with comparatively short-lasting T2D who were not on other glucose-lowering medications at the time, and approximately 50% were diabetes pharmacological treatment-naïve. Furthermore, strong HbA1c reduction was observed with the 5 mg dose in SURPASS-1, resulting in a mean HbA1c of 5.88% at the endpoint.[6] This less pronounced, dose-dependent HbA1c response in SURPASS-1 may be attributable to trial participants already achieving excellent glycaemic control with the 5 mg dose, thus limiting the possibility for glycaemia to improve further with the higher tirzepatide doses and potentially obscuring the relationship between HbA1c change and weight loss. By contrast, participants in SURPASS-5 received concomitant titrated basal insulin therapy, which may have blunted the relationship because of the known weight-gain promoting action of insulin.[18]

Across the SURPASS trials, 6%-9% of participants treated with tirzepatide 5 mg, 4%-11% of participants treated with tirzepatide 10 mg and 2%-9% of participants treated with tirzepatide 15 mg showed an improvement in HbA1c but not in body weight. While these numbers are small, this clearly shows a high degree of interindividual heterogeneity regarding body weight response, as seen previously with GLP-1 receptor agonists. This also shows that the improvements in glucose control with tirzepatide may occur independently of weight loss, which is consistent with reports that tirzepatide

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improved insulin sensitivity, also independent of weight reduction.[25] Robust improvement in glycaemic control occurring faster than weight loss and as early as 2-4 weeks of treatment in the SURPASS studies supports the notion that improvements in glycaemia involve mechanisms that are independent of weight loss.[3–7] However, additional studies are needed to further elucidate the mechanisms that may contribute to reductions in HbA1c and body weight with tirzepatide treatment.

This study has limitations. It is a post hoc analysis that is exploratory in nature. The use of different background medications across the SURPASS trials may have influenced our observations and therefore caution must be exercised during interpretation.

In conclusion, the vast majority of participants treated with tirzepatide (5, 10 and 15 mg) experienced HbA1c reduction with weight loss, across the SURPASS clinical trials, with modest, yet significant, associations between HbA1c and body weight changes in this post hoc assessment. Improvements in glycaemic control were also observed in participants who did not lose weight.

AUTHOR CONTRIBUTIONS

VTT is the guarantor of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the SURPASS studies and/or current analyses. CN was responsible for the statistical analyses. All authors participated in the interpretation of data and critical review of the manuscript, had full access to all data in the study and approved this manuscript to be submitted for publication.

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CONFLICT OF INTEREST

SDP declares personal fees for advisory board membership and speaking from Novo Nordisk, Janssen, Eli Lilly and Company, Merck, Bausch Health, AstraZeneca, Abbott, Boehringer Ingelheim, Sanofi, HLS Therapeutics and Dexcom; consulting fees from Novo Nordisk, Janssen, AstraZeneca, Abbott, HLS Therapeutics and Dexcom; fees for clinical trials from Novo Nordisk, Eli Lilly and Company, AstraZeneca, Sanofi, Prometic and Pfizer; and grants from Eli Lilly and Company, AstraZeneca, Abbott, Boehringer Ingelheim and Sanofi. GEU declares research support (to Emory University) from Dexcom, Abbott and Bayer. No potential conflicts of interest relevant to this article were reported. FG declares research support from Eli Lilly and Company and Roche Diabetes Care; consulting fees from Boehringer Ingelheim, LifeScan, Merck Sharp and Dohme, Sanofi, AstraZeneca, Medimmune, Roche Diabetes Care, Sanofi and Medtronic; and personal fees for advisory board memberships from AstraZeneca, Eli Lilly and Company, Novo Nordisk, Roche Diabetes Care and Sanofi. AR, VTT, CN, LFL, CAK and JK are employees and shareholders of Eli Lilly and Company.

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15140.

DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU 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 www.vivli.org.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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