FEATURE ARTICLE

Efficacy and Safety of Tirzepatide in Adults With Type 2 Diabetes: A Perspective for Primary Care Providers

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This article reviews the efficacy and safety data of tirzepatide, a once-weekly, novel glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 (GLP-1) receptor agonist approved in the United States, the European Union, and other regions for the treatment of type 2 diabetes. All doses of tirzepatide demonstrated superiority in reducing A1C and body weight from baseline versus placebo or active comparators. The safety profile of tirzepatide was consistent with that of the GLP-1 receptor agonist class, with mild to moderate and transient gastrointestinal side effects being the most common adverse events. With clinically and statistically significant reductions in A1C and body weight without increased risk of hypoglycemia in various populations, tirzepatide has demonstrated potential as a first-in-class treatment option for many people with type 2 diabetes.

Type 2 diabetes is a metabolic condition caused by increased insulin resistance and progressive β-cell failure in the pancreas, resulting in decreased insulin secretion and hyperglycemia. Chronic hyperglycemia can ultimately lead to both micro- and macrovascular complications, which can be prevented with appropriate glycemic control. Obesity is a major factor in the pathophysiology of type 2 diabetes; therefore, treatment of type 2 diabetes should address hyperglycemia and comorbidities (1,2).

Glucagon-like peptide 1 (GLP-1) receptor agonists are commonly used as first injectable therapy in combination with oral antihyperglycemic medications to improve and maintain glycemic control when treatment intensification is required (1,2). GLP-1 is an incretin hormone secreted by the intestine that enhances insulin secretion in response to nutrient ingestion. GLP-1 receptors are expressed in the pancreas, gastrointestinal (GI) tract, kidney, heart, and brain (3). Endogenous GLP-1 and GLP-1 receptor agonists stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner. GLP-1 receptor agonists also lead to weight loss by affecting central pathways associated with satiety.

Despite the increasing availability of innovative antihyperglycemic agents, a significant number of patients with type 2 diabetes continue to fail to reach recommended glycemic targets (4). There are also opportunities to have a stronger impact on the treatment of type 2 diabetes through the weight loss achieved with GLP-1 receptor agonists.

The metabolic effects of GLP-1 receptor agonists may be enhanced with the combined actions of another incretin hormone receptor agonist. Glucose-dependent insulinotropic polypeptide (GIP) is accountable for two-thirds of the incretin effect in healthy people (5). Unlike GLP-1 receptors, GIP receptors are expressed in adipose tissue, and preclinical data have shown that GIP can improve insulin sensitivity, lipid homeostasis, and whole-body energy metabolism (6–9). Coadministration of GIP and GLP-1, compared with the individual administration of each hormone, has shown synergistic effects in healthy people as well, significantly increasing insulin response and inhibiting glucagon secretion in the hyperglycemic and normoglycemic state, but not during hypoglycemia (10,11). Available data indicate that GIP does not stimulate insulin secretion (i.e., has no insulinotropic effect) at physiological and supraphysiological concentrations in people with type 2 diabetes (12). However, the insulinotropic effect of

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GIP can be partially restored by improving glycemic control (13). Thus, a single molecule targeting both GIP and GLP-1 receptors could potentially improve therapeutic efficacy (6,14,15), paving the way to pursue pharmacological therapies based on dual GIP and GLP-1 receptor agonism.

Tirzepatide is a 39–amino acid synthetic peptide with agonist activity at the GIP and GLP-1 receptors that has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and in other regions for the treatment of type 2 diabetes (16,17). Tirzepatide is also in development for other indications including chronic weight management. Its structure is engineered from the native GIP sequence with a C20 fatty di-acid moiety. It has a half-life of ∼5 days, enabling once-weekly subcutaneous administration (18).

A phase 1 study has shown that the mechanisms of action of tirzepatide 15 mg on glycemic control in patients with type 2 diabetes are marked improvements in α- and β-cell function (inhibition of glucagon release and increased insulin release, respectively, in a glucose-dependent manner) and in insulin sensitivity, which were significantly greater than those observed with the selective GLP-1 receptor agonist semaglutide 1 mg alone (19). Preclinical studies have shown that tirzepatide improves insulin sensitivity via weight-dependent and weight-independent mechanisms, the latter attributable to the GIP receptor agonism (7). There was also evidence of increase in energy expenditure in mice after 1 week of treatment with tirzepatide, which may contribute to sustained body weight loss (18). Further studies are needed to evaluate these potential mechanisms of action in humans.

A phase 2 study assessed the efficacy and safety of four doses (1, 5, 10, and 15 mg) of tirzepatide versus placebo and an active comparator (once-weekly dulaglutide 1.5 mg) in patients with type 2 diabetes (20). The study demonstrated the superiority of tirzepatide 5, 10, and 15 mg versus placebo and dulaglutide 1.5 mg in decreasing A1C at week 26. Likewise, tirzepatide 5, 10, and 15 mg were superior to placebo in body weight reduction, and tirzepatide 10 and 15 mg were superior to dulaglutide 1.5 mg in body weight reduction. Similar to the tirzepatide phase 1 study (18), most of the tirzepatide adverse events (AEs) were GI-related, with the incidence higher than that for the GLP-1 receptor agonist class.

Additionally, a placebo-controlled, phase 2 study assessed the efficacy and tolerability of tirzepatide treatment using three different escalation schemes with longer time intervals between dose escalations and different dose escalations to attain doses as high as 15 mg in patients with type 2 diabetes (21). The findings from this study suggested that a gradual dose escalation regimen, with smaller dose increments, is associated with a more favorable GI side effect profile and supported the evaluation of optimized dosing regimen(s) in phase 3.

In this review, we summarize the clinical evidence for tirzepatide to improve glycemic control in people with type 2 diabetes from five completed global studies of the phase 3 SURPASS program: SURPASS-1 through SURPASS-5 (22–26).

Overview of the Study Design Across the Completed SURPASS Trials

The aim of the SURPASS clinical trial program was to assess the efficacy and safety of three doses of tirzepatide (5, 10, and 15 mg) once weekly in participants with type 2 diabetes. Based on the findings of the phase 2 studies, the dose escalation scheme in the SURPASS trials was as follows: all doses started at 2.5 mg once weekly for 4 weeks; then each dose was escalated every 4 weeks in increments of 2.5 mg until the corresponding maintenance dose of tirzepatide (5, 10, or 15 mg) was attained and maintained for the remainder of the study (Figure 1).

Tirzepatide was compared with placebo as monotherapy in SURPASS-1 (NCT03954834) during 40 weeks of treatment. Tirzepatide was also assessed versus placebo or active comparators as add-on to different background antihyperglycemic medications: versus once-weekly GLP-1 receptor agonist semaglutide 1 mg as add-on to metformin for 40 weeks in SURPASS-2 (NCT03987919); versus once-daily insulin degludec as add-on to metformin with or without a sodium–glucose cotransporter 2 (SGLT2) inhibitor for 52 weeks in SURPASS-3 (NCT03882970); versus once-daily insulin glargine as add-on to any combination of metformin, sulfonylurea, and SGLT2 inhibitor for 52 weeks plus a variable treatment period of up to 52 weeks in SURPASS-4 (NCT03730662); and versus placebo as add-on to insulin glargine with or without metformin for 40 weeks in SURPASS-5 (NCT04039503). All five studies were randomized trials with a 1:1:1:1 ratio for tirzepatide 5, 10, or 15 mg, or placebo/active comparator, except SURPASS-4, which had a 1:1:1:3 ratio. SURPASS-1 and SURPASS-5 were double-blind trials, whereas SURPASS-2, SURPASS-3, and SURPASS-4 were open-label trials.

The primary efficacy end point for these studies was the change from baseline in A1C. Secondary efficacy end points included the proportion of participants with an

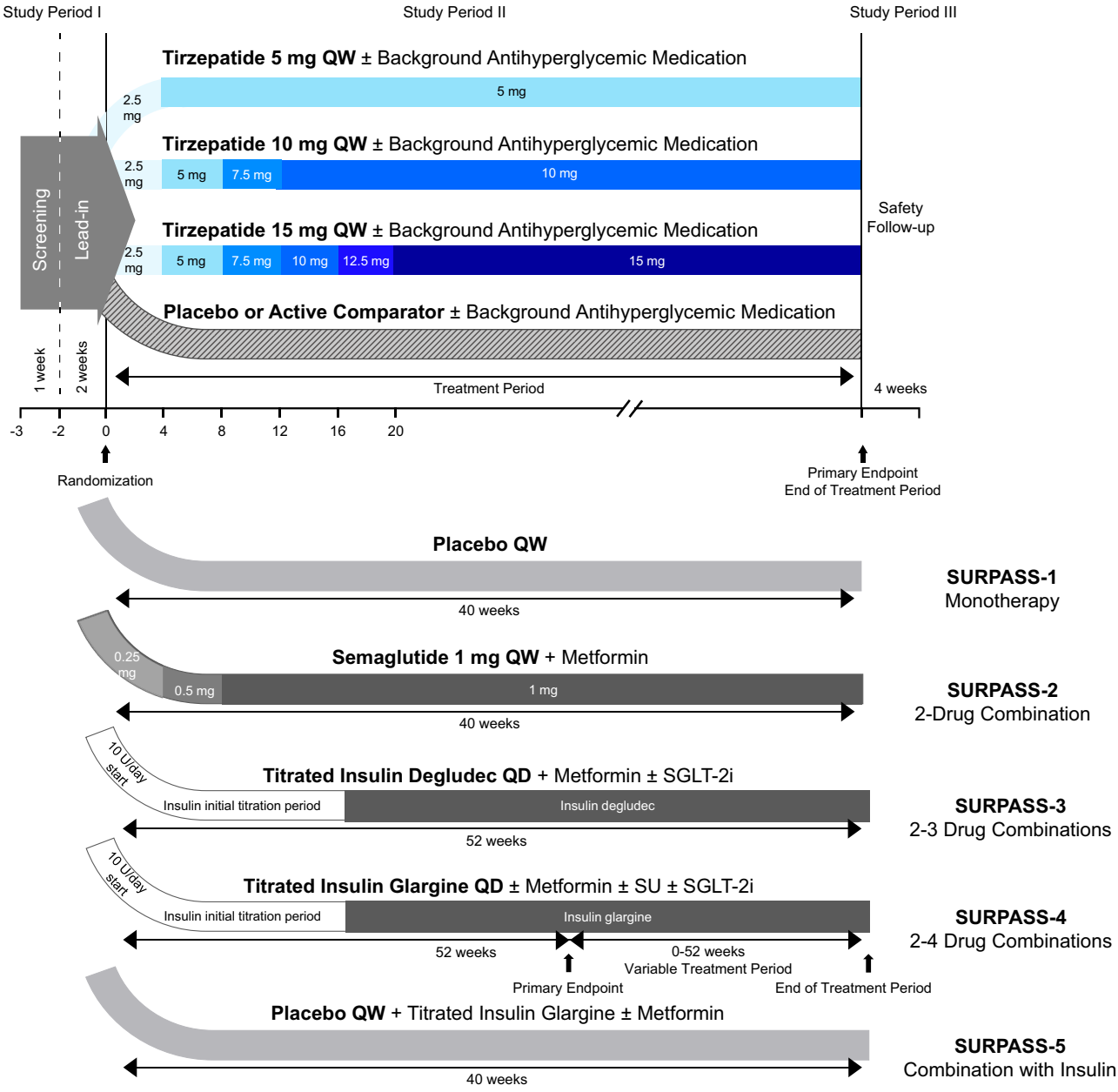

FIGURE 1 Overview of the study design across the completed SURPASS trials. Each dose of tirzepatide was initiated at 2.5 mg once weekly for 4 weeks and escalated every 4 weeks in increments of 2.5 mg until the corresponding maintenance dose was achieved. SGLT-2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; QD, once daily; QW, once weekly.

A1C <7.0% (53 mmol/mol), ≤6.5% (48 mmol/mol), and <5.7% (39 mmol/mol); mean change from baseline in body weight; and proportion of participants reaching ≥5%, ≥10%, and ≥15% weight loss.

Baseline Demographics and Clinical Characteristics

The numbers of participants randomized and included in the modified intention-to-treat population (i.e., all participants who received at least one dose of study drug) in the placebo-controlled trials (SURPASS-1 and SURPASS-5) were 478 and 475, respectively, and 1,878, 1,437, and 1,995 in the active-controlled trials (SURPASS-2, SURPASS-3, and SURPASS-4, respectively). The mean age of participants ranged from 54 years in SURPASS-1 to 64 years in SURPASS-4 (Table 1). The number of males/females was balanced across the five trials. Because of the global nature of the SURPASS program and the countries participating in it, the majority of participants in each of the five studies were White, and the proportions of Black

TABLE 1 Summary of Baseline Demographics and Clinical Characteristics From the Completed SURPASS Trials

Characteristic	SURPASS-1 (*N* = 478)	SURPASS-2 (*N* = 1,878)	SURPASS-3 (*N* = 1,437)	SURPASS-4 (*N* = 1,995)	SURPASS-5 (*N* = 475)
Age, years	54.1 ± 11.9	56.6 ± 10.4	57.4 ± 10.0	63.6 ± 8.6	60.6 ± 9.9
Sex					
Male	247 (52)	882 (47)	802 (56)	1,246 (62)	264 (56)
Female	231 (48)	996 (53)	635 (44)	749 (38)	211 (44)
Race					
American Indian or Alaska Native	118 (25)	208 (11)	4 (<1)	173 (9)	2 (<1)
Asian	168 (35)	25 (1)	76 (5)	70 (4)	85 (18)
Black or African American	22 (5)	79 (4)	44 (3)	73 (4)	6 (1)
Multiple	–	12 (1)	2 (<1)	43 (2)	2 (<1)
Native Hawaiian or other Pacific Islander	–	3 (<1)	4 (<1)	3 (<1)	–
White	170 (36)	1,551 (83)	1,307 (91)	1,629 (82)	380 (80)
Ethnic origin					
Hispanic or Latino	207 (43)	1,317 (70)	421 (29)	950 (48)	22 (5)
Not Hispanic or Latino	184 (38)	561 (30)	1,009 (70)	1,030 (52)	380 (80)
Not reported	87 (18)	–	7 (1)	15 (1)	73 (15)
Duration of type 2 diabetes, years	4.7 ± 5.4	8.6 ± 6.5	8.4 ± 6.2	11.8 ± 7.5	13.3 ± 7.3
A1C					
Values, %	7.94 ± 0.87	8.28 ± 1.03	8.17 ± 0.91	8.52 ± 0.88	8.31 ± 0.85
Values, mmol/mol	63.29 ± 9.46	67.03 ± 11.25	65.78 ± 9.99	69.65 ± 9.65	67.38 ± 9.31
≤8.5% (≤8.0% for SURPASS-5)	378 (79)	1,192 (64)	1,005 (70)	1,131 (57)	201 (42)
>8.5% (>8.0% for SURPASS-5)	100 (21)	686 (37)	432 (30)	864 (43)	273 (58)
Fasting serum glucose					
Values, mmol/L	8.53 ± 2.21	9.60 ± 2.86	9.40 ± 2.55	9.50 ± 2.82	9.01 ± 2.85
Values, mg/dL	153.6 ± 39.8	172.9 ± 51.5	169.3 ± 45.9	171.2 ± 50.8	162.4 ± 51.3
Diabetes medication at randomization*					
Metformin alone	–	1,878 (100)	979 (68)	639 (32)	–
Sulfonylurea alone	–	–	–	74 (4)	–
SGLT-2i alone	–	–	–	12 (1)	–
Metformin + sulfonylurea	–	–	–	780 (39)	–
Metformin + SGLT-2i	–	–	458 (32)	257 (13)	–
Metformin + sulfonylurea + SGLT-2i	–	–	–	217 (11)	–
Insulin glargine alone	–	–	–	–	81 (17)
Insulin glargine + metformin	–	–	–	–	394 (83)
Body weight, kg	85.9 ± 19.8	93.7 ± 21.9	94.3 ± 20.1	90.3 ± 18.7	95.2 ± 21.6
BMI, kg/m^2	31.9 ± 6.6	34.2 ± 6.9	33.5 ± 6.1	32.6 ± 5.5	33.4 ± 6.1
Blood pressure, mmHg					
Systolic	127.6 ± 14.1	130.6 ± 13.8	131.5 ± 13.3	134.4 ± 15.4	137.9 ± 15.7
Diastolic	79.4 ± 8.8	79.2 ± 9.0	79.2 ± 8.9	78.4 ± 9.4	80.7 ± 10.8
Pulse rate, bpm	73.7 ± 9.4	74.8 ± 10.1	75.2 ± 9.7	72.8 ± 10.5	75.2 ± 11.2
eGFR (CKD-EPI calculation), mL/min/1.73 m^2	94.1 ± 19.7	96.0 ± 17.1	94.1 ± 17.0	81.3 ± 21.1	85.5 ± 17.8
<60	28 (6)	64 (3)	56 (4)	342 (17)	47 (10)
≥60	450 (94)	1,814 (97)	1,381 (96)	1,653 (83)	428 (90)

Data are mean ± SD or *n* (%) for all randomly assigned participants who took at least one dose of study drug (modified intention-to-treat population). Percentages might not sum to 100 because of rounding. *Metformin doses ≥1,500 mg/day; insulin glargine doses 37.6 units/day (SD 22.7 units/day) or 0.40 units/kg/day (SD 0.23 units/kg/day). CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; SGLT-2i, sodium–glucose cotransporter 2 inhibitor.

or African American participants were 1−5%. In the U.S. trial sites, the proportion of Black or African American participants was 13−22%. In SURPASS-1, the proportion of White participants was relatively lower (36%), whereas the proportions of Asian (35%) and American Indian or Alaska Native (25%) participants were relatively higher compared with the other SURPASS studies. The reported Hispanic or Latino population ranged from 5% in SURPASS-5 to 70% in SURPASS-2.

The mean A1C concentration at baseline ranged from 7.9% in SURPASS-1, with a relatively shorter mean duration of type 2 diabetes (4.7 years) in this younger population, to 8.5% in SURPASS-4, with a relatively longer mean duration of the disease (11.8 years) in participants with increased cardiovascular (CV) risk (87% with a history of CV disease). The overall population of SURPASS-1 had the lowest BMI (31.9 kg/m^2) and body weight (85.9 kg) at baseline, whereas these parameters were slightly higher in the rest of the SURPASS studies (33−34 kg/m^2 and 90−95 kg).

Efficacy of Tirzepatide

Efficacy data presented herein are based on the efficacy estimand, which represents on-treatment efficacy, including all randomized participants who continued to receive the study drug without rescue medication. A summary of the efficacy results across the completed SURPASS trials is presented in Table 2 and Figure 2*A* and *B*.

The A1C reduction from baseline to the primary end point ranged from −1.87% with tirzepatide 5 mg in SURPASS-1 to −2.59% with tirzepatide 10 and 15 mg in SURPASS-5, considering the different participant populations, background antihyperglycemic medications, and durations of the studies. The A1C reductions were significantly greater in each SURPASS trial for all tirzepatide doses compared with placebo (SURPASS-1 and SURPASS-5) or active comparators semaglutide 1 mg (SURPASS-2) or basal insulin (SURPASS-3 and SURPASS-4) at the primary end point (Table 2 and Figure 2*A*). This effect was sustained in SURPASS-4 through the end of the variable treatment period (up to week 104) (25).

The American Diabetes Association (ADA) recommends an A1C target of ≤7% (53 mmol/mol) for most nonpregnant adults with type 2 diabetes and enough life expectancy to observe beneficial effects on microvascular outcomes (∼10 years) (1,27). Glycemic values must be personalized based on patient preference, risk of hypoglycemia and other AEs of therapy, and patient comorbidities.

The proportion of participants achieving an A1C value <7.0%, ≤6.5%, or <5.7% with tirzepatide across the completed SURPASS trials ranged from 81 to 97%, from 66 to 95%, and from 23 to 62%, respectively (Table 2). Significantly more participants achieved the three A1C values with all tirzepatide doses in each of the five SURPASS studies compared with placebo or active comparators at the primary end point.

Body weight loss in the treatment of type 2 diabetes is paramount, as excess body weight and obesity are linked to CV health and comorbidities. In addition, weight gain can discourage patients from initiating therapy. Therefore, broadening the treatment continuum with therapies that achieve glycemic control with weight loss effects is important. In the SURPASS trials, body weight reductions from baseline at the primary end point ranged from −6.2 kg (−6.6%) with tirzepatide 5 mg when added to insulin glargine (SURPASS-5) to −12.9 kg (−13.9%) with tirzepatide 15 mg when added to metformin with or without an SGLT2 inhibitor (SURPASS-3) (Table 2 and Figure 2*B*). In each of the SURPASS clinical trials, body weight reductions were significantly greater for all tirzepatide doses compared with placebo or the active comparators, including semaglutide 1 mg (SURPASS-2). In fact, weight gain was observed with basal insulin (SURPASS-3 and SURPASS-4) and with placebo in combination with insulin glargine (SURPASS-5). Tirzepatide-induced body weight loss effect was gradual up to the primary end point (40 or 52 weeks) across all SURPASS trials and was sustained through the end of the variable treatment period (up to week 104) in SURPASS-4 (25). Because SGLT2 inhibitors have favorable effects on weight, the concomitant use of an SGLT2 inhibitor with tirzepatide in SURPASS-3 may raise the question of whether tirzepatide was solely responsible for the greatest extent of weight loss observed in the SURPASS program. Subgroup analyses in SURPASS-3 showed that the reductions in body weight were similar regardless of the concomitant use of an SGLT2 inhibitor (24).

According to ADA guidelines, in patients with type 2 diabetes, a 5% weight loss is needed to achieve beneficial effects on glucose, lipids, and blood pressure levels, and these benefits can be maximized with more intensive weight loss of 15% (28). The proportion of participants achieving a weight loss of ≥5%, ≥10%, or ≥15% with tirzepatide across the completed SURPASS trials ranged from 54 to 88%, from 23 to 69%, and from 7 to 43%, respectively (Table 2). Significantly more participants achieved the weight loss of ≥5%, ≥10%, or ≥15% with all tirzepatide doses in each of the

TABLE 2 Summary of the Efficacy Outcomes at Primary End point of the Completed SURPASS Trials

	N	Δ in A1C, %	Participants Achieving A1C Values, %			Δ in Body Weight, kg (%)	Participants Achieving Weight Loss Values, %		
			<7.0%	≤6.5%	<5.7%		≥5%	≥10%	≥15%
SURPASS-1, monotherapy (primary end point at week 40)									
Tirzepatide 5 mg	121	−1.87‡**	87‡**	82**	34‡**	−7.0‡** (−7.9)	67**	31**	13*
Tirzepatide 10 mg	121	−1.89‡**	92‡**	81**	31‡**	−7.8‡** (−9.3)	78**	40**	17*
Tirzepatide 15 mg	120	−2.07‡**	88‡**	86**	52‡**	−9.5‡** (−11.0)	77**	47**	27*
Placebo	113	0.04	19	10	1	−0.7 (−0.9)	14	1	0
SURPASS-2, add-on to metformin (primary end point at week 40)									
Tirzepatide 5 mg	470	−2.09†**	85‡*	74*	29**	−7.8‡** (−8.5)	69*	36**	15*
Tirzepatide 10 mg	469	−2.37†**	89‡**	82**	45‡**	−10.3‡** (−11.0)	82**	53**	28**
Tirzepatide 15 mg	469	−2.46†**	92‡**	87**	51‡**	−12.4‡** (−13.1)	86**	65**	40**
Semaglutide 1 mg	468	−1.86	81	66	20	−6.2 (−6.7)	58	25	9
SURPASS-3, add-on to metformin ± SGLT-2i (primary end point at week 52)									
Tirzepatide 5 mg	358	−1.93†‡**	82‡**	71**	26**	−7.5‡** (−8.1)	66**	37**	13**
Tirzepatide 10 mg	360	−2.20†‡**	90‡**	80**	39**	−10.7‡** (−11.4)	84**	56**	28**
Tirzepatide 15 mg	358	−2.37†‡**	93‡**	85**	48**	−12.9‡** (−13.9)	88**	69**	43**
Insulin degludec	359	−1.34	61	44	5	2.3 (2.7)	6	3	0
SURPASS-4, add-on to metformin ± sulfonylurea ± SGLT-2i (primary end point at week 52)									
Tirzepatide 5 mg	326	−2.24†**	81‡**	66**	23**	−7.1‡** (−8.1)	63**	36**	14**
Tirzepatide 10 mg	321	−2.43†**	88‡**	76**	33**	−9.5‡** (−10.7)	78**	53**	24**
Tirzepatide 15 mg	334	−2.58†**	91‡**	81**	43**	−11.7‡** (−13.0)	85**	66**	37**
Insulin glargine	978	−1.44	51	32	3	1.9 (2.2)	8	2	<1
SURPASS-5, add-on to insulin glargine ± metformin (primary end point at week 40)									
Tirzepatide 5 mg	116	−2.23‡**	93‡**	80**	26**	−6.2‡** (−6.6)	54**	23**	7*
Tirzepatide 10 mg	119	−2.59‡**	97‡**	95**	48‡**	−8.2‡** (−8.9)	65**	47**	27*
Tirzepatide 15 mg	120	−2.59‡**	94‡**	92**	62‡**	−10.9‡** (−11.6)	85**	51**	32**
Placebo	120	−0.93	34	17	3	1.7 (1.7)	6	1	0

All data are for the efficacy estimand, including all randomized participants who continued to receive the study drug without rescue medication. Change from baseline data are least squares mean from mixed-model repeated measures analysis. †Tested for noninferiority versus placebo or active comparator, controlled for type 1 error. ‡Tested for superiority versus placebo or active comparator, controlled for type 1 error. *P <0.05 tirzepatide versus placebo or active comparator. **P <0.001 for tirzepatide versus placebo or active comparator. Δ, mean change from baseline; SGLT-2i, sodium–glucose cotransporter 2 inhibitor.

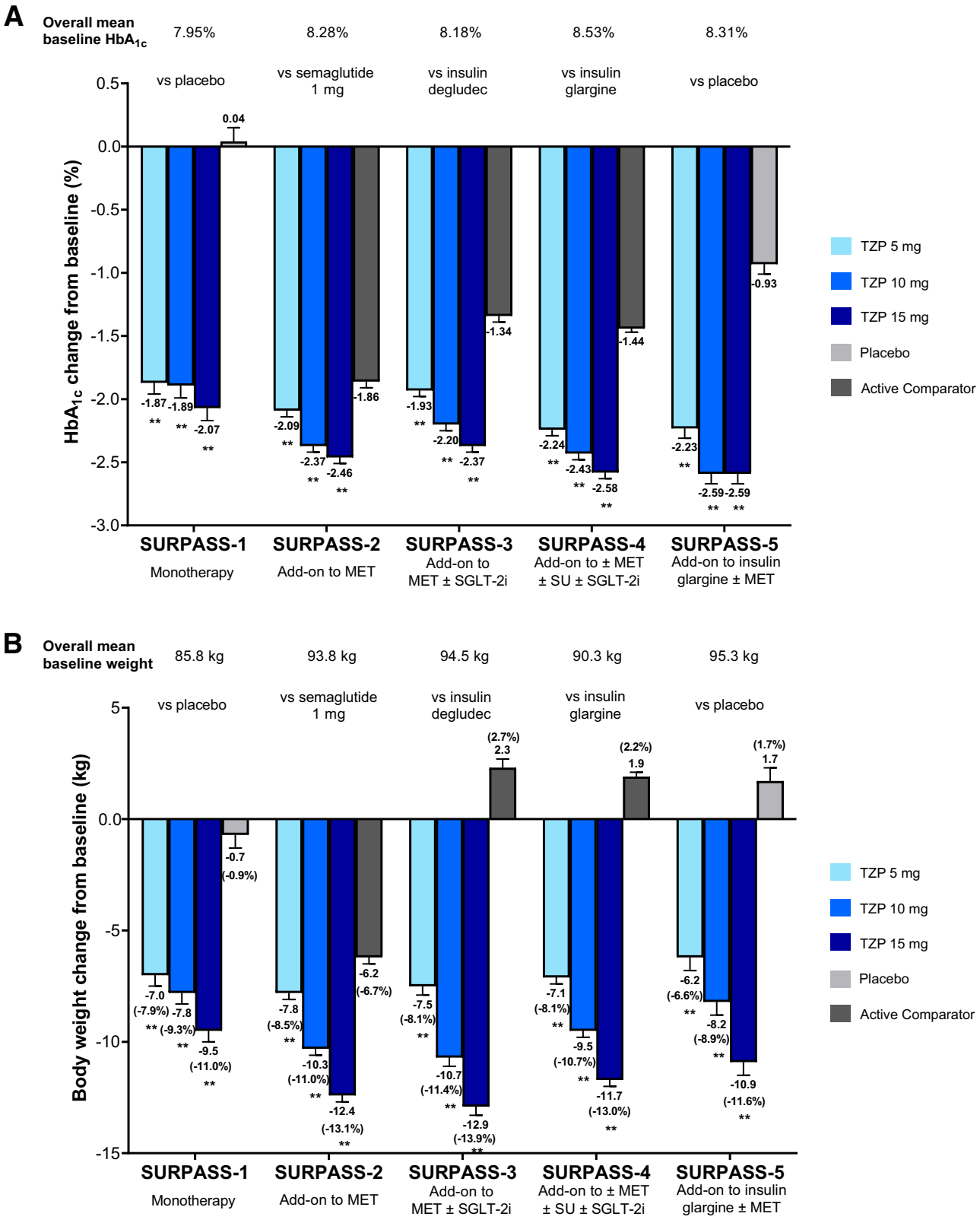

FIGURE 2 Change from baseline in A1C (*A*) and body weight (*B*) at primary end point of the completed SURPASS trials. All data are for the efficacy estimand, including all randomized participants who continued to receive the study drug without rescue medication. Change from baseline data are least squares mean (error bars are SE) from mixed-model repeated measures analysis. Primary end point was 40 weeks for SURPASS-1, SURPASS-2, and SURPASS-5, and 52 weeks for SURPASS-3 and SURPASS-4. $^{**}P < 0.001$ for tirzepatide versus placebo or active comparator. HbA_{1c}, hemoglobin A_{1c}; MET, metformin; SGLT-2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZP, tirzepatide.

five SURPASS studies compared with placebo or active comparators at the primary end point.

There was an overall improvement in the fasting lipid profile with tirzepatide across the SURPASS trials. Namely, there was a decrease from baseline in triglycerides (by 15.2−26.7%), LDL cholesterol (by 5.2−15.5%), and VLDL cholesterol (by 14.2−25.2%) and an increase from baseline in HDL cholesterol (by 0.9−10.8%) with all tirzepatide doses at the primary end point. Decreases in systolic (of 2.8−12.6 mmHg) and diastolic (of 0.8−4.5 mmHg) blood pressure were also observed with tirzepatide in all SURPASS trials. Moreover, decreases in ALT and AST were observed with tirzepatide across the trials in which these measures were reported (SURPASS-1, SURPASS-2, SURPASS-3, and SURPASS-5). Furthermore, a specific MRI substudy was performed in the SURPASS-3 trial, and the results showed significant improvements in liver fat content and abdominal adipose tissue with all doses of tirzepatide in a subpopulation with type 2 diabetes and higher risk of elevated liver fat content (29). All of this evidence supports the potential role of tirzepatide in fatty liver disease and chronic weight management, which will be further explored in studies specifically designed for that purpose (e.g., the SYNERGY-NASH trial [NCT04166773] and the SURMOUNT program, respectively).

In SURPASS-5, insulin glargine 100 units/mL was administered as background antihyperglycemic medication once daily after an initial 4-week insulin stabilization period and a 36-week insulin titration period (26). During the insulin stabilization period, the dose of insulin glargine was unchanged except for safety reasons and additionally reduced by 20% in participants with an A1C ≤8.0% at randomization to minimize the risk of hypoglycemia. During the insulin titration period, the dose of insulin glargine was self-adjusted to a target fasting blood glucose of <100 mg/dL following a treat-to-target algorithm. Further details on the insulin titration algorithm used in SURPASS-5 can be found in Supplementary Table S1. At the primary end point (week 40), the mean change from baseline in insulin glargine dose was 4.4 units for tirzepatide 5 mg, 2.7 units for tirzepatide 10 mg, −3.8 units for tirzepatide 15 mg, and 25.1 units for placebo. This markedly lower use of insulin glargine in the tirzepatide arms versus placebo (P <0.001 for all tirzepatide doses in percentage change) was associated with the superior glycemic outcomes observed with tirzepatide.

Safety of Tirzepatide

In general, the proportion of participants reporting AEs was similar across all treatment groups in the five SURPASS trials (Table 3). The incidence of serious AEs was <20% across all treatment arms in all of the trials. There were no deaths in SURPASS-5, one (<1%) in SURPASS-1, five (<1%) in SURPASS-3, 13 (1%) in SURPASS-2, and 60 (3%) in SURPASS-4. None of the deaths were considered by the investigators to be related to the study treatment.

Overall, treatment discontinuation because of AEs was low in all SURPASS trials and more common in the tirzepatide groups (3−11%) versus placebo (3%; SURPASS-1 and SURPASS-5), versus semaglutide 1 mg (4%; SURPASS-2), and versus basal insulin (1% and 5%; SURPASS-3 and SURPASS-4, respectively). GI AEs were the most common reason for treatment discontinuation in tirzepatide-treated participants.

Nausea, diarrhea, decreased appetite, and vomiting were the most frequent treatment-emergent AEs in the tirzepatide groups across all SURPASS trials and in the semaglutide 1 mg group in SURPASS-2 (Table 3). The incidence of these GI AEs throughout each study period was higher in the tirzepatide groups (12−24% for nausea, 12−22% for diarrhea, 4−14% for decreased appetite, and 2−13% for vomiting) compared with placebo (SURPASS-1 and SURPASS-5) and basal insulin (SURPASS-3 and SURPASS-4), and similar in tirzepatide and semaglutide 1 mg (SURPASS-2). Most cases of nausea, diarrhea, and vomiting were mild to moderate in severity, with the highest incidence observed during the dose escalation period and then decreasing over time. As an example, the incidence of nausea over 40 weeks in the SURPASS-2 trial showed a comparable profile for tirzepatide and semaglutide 1 mg (Figure 3). Further details on the incidence of nausea, diarrhea, and vomiting over time for tirzepatide are published in the literature (22–26). The optimized slow dose escalation scheme used in the phase 3 SURPASS program improved the GI tolerability of tirzepatide compared with the phase 2 trials. The GI tolerability of tirzepatide was similar to that of selective GLP-1 receptor agonists.

There were no cases of severe or clinically significant hypoglycemia (blood glucose <54 mg/dL) in the tirzepatide groups in SURPASS-1 (monotherapy) and 0 or 1% with placebo, respectively (Table 3). A very low proportion of tirzepatide-treated participants reported severe (0−1%) or clinically significant hypoglycemia (<1−9%) in SURPASS-2, SURPASS-3, and SURPASS-4 (add-on to oral antihyperglycemic medications). The hypoglycemia incidence was numerically higher in SURPASS-5, as expected, as the study treatment was administered in combination with basal insulin. However, no differences were noted in severe or clinically significant hypoglycemia

TABLE 3 Summary of AEs in the Completed SURPASS Trials

	N	Serious AEs	Deaths*	AEs Leading to Treatment Discontinuation	≥1 Treatment-Emergent AE	Most Frequent GI AEs†				Hypoglycemia‡	
						Nausea	Diarrhea	Decreased Appetite	Vomiting	Blood Glucose <54 mg/dL	Severe
SURPASS-1, monotherapy (primary end point at week 40)											
Tirzepatide 5 mg	121	5 (4)	0 (0)	4 (3)	83 (69)	14 (12)	14 (12)	5 (4)	4 (3)	0 (0)	0 (0)
Tirzepatide 10 mg	121	2 (2)	0 (0)	6 (5)	81 (67)	16 (13)	17 (14)	8 (7)	3 (2)	0 (0)	0 (0)
Tirzepatide 15 mg	121	1 (1)	0 (0)	8 (7)	77 (64)	22 (18)	14 (12)	10 (8)	7 (6)	0 (0)	0 (0)
Placebo	115	3 (3)	1 (1)	3 (3)	76 (66)	7 (6)	9 (8)	1 (1)	2 (2)	1 (1)	0 (0)
SURPASS-2, add-on to metformin (primary end point at week 40)											
Tirzepatide 5 mg	470	33 (7)	4 (1)	28 (6)	299 (64)	82 (17)	62 (13)	35 (7)	27 (6)	3 (1)	1 (<1)
Tirzepatide 10 mg	469	25 (5)	4 (1)	40 (9)	322 (69)	90 (19)	77 (16)	34 (7)	40 (9)	1 (<1)	0 (0)
Tirzepatide 15 mg	470	27 (6)	4 (1)	40 (9)	324 (69)	104 (22)	65 (14)	42 (9)	46 (10)	8 (2)	1 (<1)§
Semaglutide 1 mg	469	13 (3)	1 (<1)	19 (4)	301 (64)	84 (18)	54 (12)	25 (5)	39 (8)	2 (<1)	0 (0)
SURPASS-3, add-on to metformin ± SGLT-2i (primary end point at week 52)											
Tirzepatide 5 mg	358	29 (8)	1 (<1)	25 (7)	219 (61)	41 (12)	55 (15)	22 (6)	21 (6)	5 (1)	0 (0)
Tirzepatide 10 mg	360	20 (6)‖	2 (1)	37 (10)	248 (69)	81 (23)	60 (17)	37 (10)	34 (9)	4 (1)	0 (0)
Tirzepatide 15 mg	359	26 (7)	1 (<1)	39 (11)	263 (73)	85 (24)	56 (16)	43 (12)	36 (10)	7 (2)	1 (<1)
Insulin degludec	360	22 (6)	1 (<1)	5 (1)	193 (54)	6 (2)	14 (4)	2 (1)	4 (1)	26 (7)	0 (0)
SURPASS-4, add-on to metformin ± sulfonylurea ± SGLT-2i (primary end point at week 52)											
Tirzepatide 5 mg	329	48 (15)	15 (5)	37 (11)	232 (71)	39 (12)	41 (13)	29 (9)	16 (5)	29 (9)	1 (<1)
Tirzepatide 10 mg	328	54 (17)	2 (<1)	28 (9)	241 (74)	53 (16)	65 (20)	36 (11)	27 (8)	20 (6)	0 (0)
Tirzepatide 15 mg	338	41 (12)	8 (2)	36 (11)	259 (77)	76 (23)	74 (22)	35 (10)	29 (9)	27 (8)	3 (1)
Insulin glargine	1,000	193 (19)	35 (4)	54 (5)	679 (68)	23 (2)	44 (4)	5 (<1)	16 (2)	191 (19)	11 (1)

Continued on p. 267 »

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TABLE 3 Summary of AEs in the Completed SURPASS Trials (Continued)

	N	Serious AEs	Deaths*	AEs Leading to Treatment Discontinuation	≥1 Treatment-Emergent AE	Most Frequent GI AEs†				Hypoglycemia‡	
						Nausea	Diarrhea	Decreased Appetite	Vomiting	Blood Glucose <54 mg/dL	Severe
SURPASS-5, add-on to insulin glargine ± metformin (primary end point at week 40)											
Tirzepatide 5 mg	116	9 (8)	0 (0)	7 (6)	85 (73)	15 (13)	14 (12)	8 (7)	8 (7)	18 (16)	0 (0)
Tirzepatide 10 mg	119	13 (11)	0 (0)	10 (8)	81 (68)	21 (18)	15 (13)	15 (13)	9 (8)	23 (19)	2 (2)
Tirzepatide 15 mg	120	9 (8)	0 (0)	13 (11)	94 (78)	22 (18)	25 (21)	17 (14)	15 (13)	17 (14)	1 (1)
Placebo	120	10 (8)	0 (0)	3 (3)	81 (68)	3 (3)	12 (10)	2 (2)	3 (3)	15 (13)	0 (0)

Data are *n* (%) in the safety population (modified intention-to-treat population, using all data from the start of treatment to the end of the safety follow-up period). Participants might be counted in more than one category. *Deaths are also included as serious AEs and discontinuations due to AEs. No deaths were considered by the investigators to be related to the study treatment. All deaths were adjudicated by an external committee of physicians with cardiology expertise. †Preferred term per the *Medical Dictionary for Regulatory Activities*. ‡Data excluding hypoglycemic events occurring after initiation of new antihyperglycemic therapy. Severe hypoglycemia was defined as an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. §This patient had a hypoglycemic event that was not considered by the investigator to be severe, but it was reported as a serious AE. ||One serious AE included here is not valid because it occurred before randomization. SGLT-2i, sodium–glucose cotransporter 2 inhibitor.

between the tirzepatide and placebo groups. Therefore, no increased risk of hypoglycemia was associated with tirzepatide versus comparators in any of the SURPASS trials. These findings are consistent with those for drugs in the GLP-1 receptor agonist class, which have an inherently low propensity to induce hypoglycemia because of their glucose-dependent mechanism of action. An ongoing phase 1 trial (NCT04050553) is investigating the effect of tirzepatide on the counterregulatory response to hypoglycemia.

No cases of treatment-emergent diabetic retinopathy were reported in SURPASS-1 or SURPASS-5, and very few cases were reported in SURPASS-2 (<1% with tirzepatide 10 mg), SURPASS-3 (1% with tirzepatide 5 mg and <1% with tirzepatide 15 mg), and SURPASS-4 (<1% in all treatment groups) (Supplementary Table S2). Of note, all SURPASS trials excluded participants with a history of proliferative diabetic retinopathy, diabetic maculopathy, or nonproliferative diabetic retinopathy requiring acute treatment. A substudy of the ongoing SURPASS-CVOT trial (NCT04255433) will investigate diabetic retinopathy progression on tirzepatide in a subpopulation with or at increased risk for diabetic retinopathy.

Very few cases of malignant neoplasms were reported in SURPASS-3 (up to 1%) and SURPASS-5 (up to 2%) across all treatment groups (24,26). No cases of medullary thyroid cancer were reported in any of the five SURPASS trials (22–26). There were no clinically relevant changes from baseline in mean calcitonin levels during any of the SURPASS trials.

One case (1%) of pancreatic cancer was reported in the tirzepatide 5 mg group in SURPASS-1. No cases of adjudicated pancreatitis were reported in SURPASS-1, SURPASS-3, or SURPASS-5, whereas it was reported in up to 1% of participants in SURPASS-2 and SURPASS-4 across all treatment groups (Supplementary Table S2). None of these cases were serious in SURPASS-2. It should be considered that participants with a history of pancreatitis were excluded from the five SURPASS trials.

Heart rate increases of up to 5.6 bpm were observed with tirzepatide at the primary end point, which is consistent with those seen with GLP-1 receptor agonists. To assess the CV safety of tirzepatide, a meta-analysis was performed following the FDA and the EMA guidance (30–32). Pooled data from the five SURPASS trials reviewed herein were included in the CV safety meta-analysis, in addition to data from one phase 2 trial and one regional phase 3 trial in Japan. Results from the

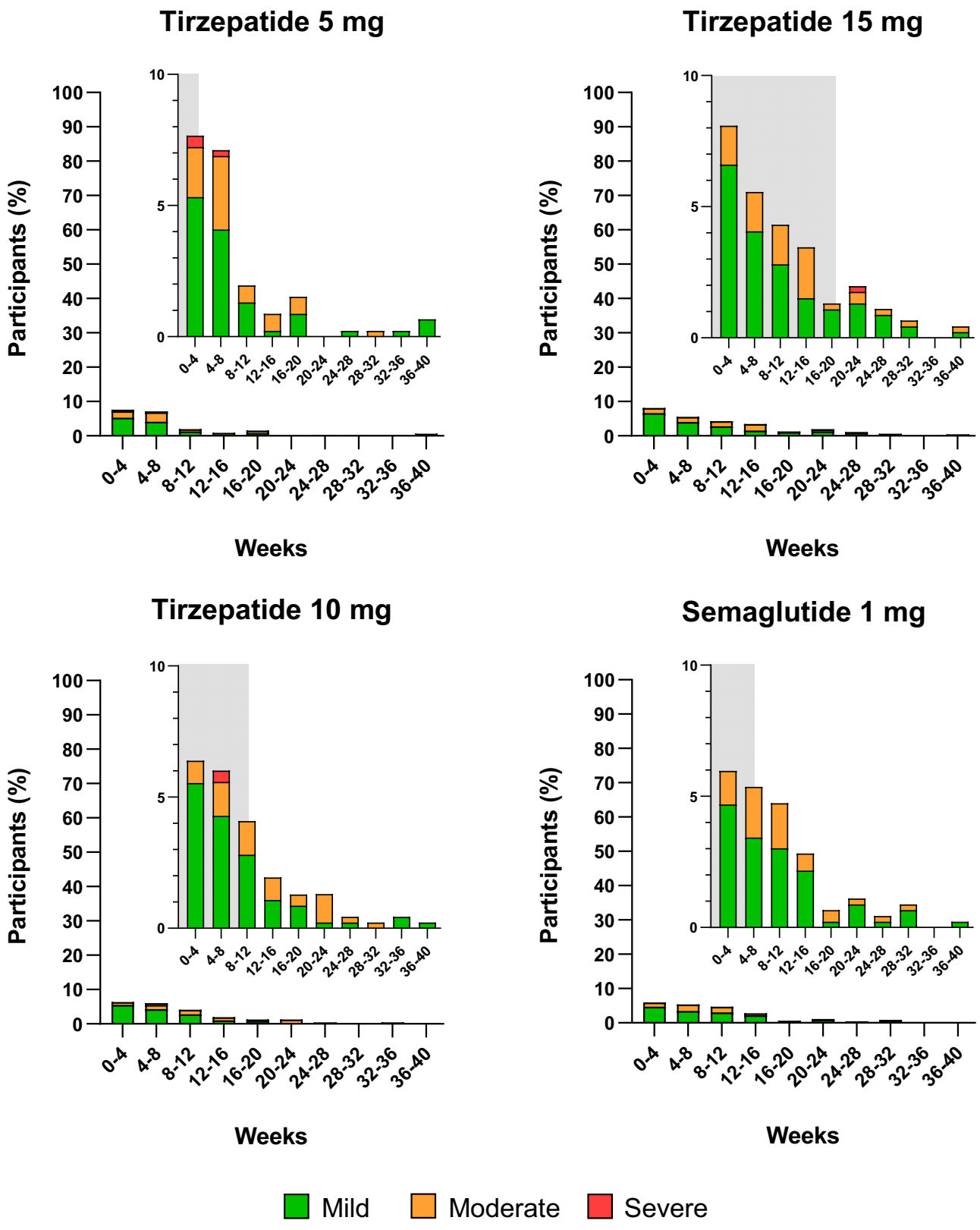

FIGURE 3 Incidence of nausea over time in SURPASS-2. Data are percentage of participants who reported a new event relative to participants at risk during a time interval in the safety population (modified intention-to-treat population using all data from the start of treatment to the end of the safety follow-up period). Gray shaded areas indicate the period of time before initiating the maintenance doses of the study treatment. Incidence refers to the proportion of participants who had a new event during a time interval.

meta-analysis indicate that tirzepatide is not associated with an increased risk of major CV events in people with type 2 diabetes (33). The hazard ratio comparing tirzepatide versus comparators was 0.80 (95% CI 0.57–1.11) for confirmed four-component major adverse CV events, including CV death, myocardial infarction, stroke, and hospitalization for unstable angina. The ongoing long-term SURPASS-CVOT trial (NCT04255433) will further assess CV safety and efficacy of tirzepatide compared with the selective GLP-1 receptor agonist dulaglutide 1.5 mg, providing a more comprehensive evaluation of the potential cardioprotective effects. This is the first CV outcomes trial comparing the CV efficacy of a novel antihyperglycemic medication for type 2 diabetes with an active comparator with proven, product-labeled CV efficacy.

Injection site reactions and hypersensitivity reactions occurred in <1–7% and 1–7%, respectively, of tirzepatide-treated participants across all SURPASS trials (Supplementary Table S2). No severe cases of hypersensitivity and injection site reactions were reported (22–24,26). Overall, the samples of tirzepatide-treated participants with treatment-emergent antidrug antibodies detected had similar pharmacokinetics and efficacy to the samples of participants with treatment-emergent antidrug antibodies not detected (22,24,25).

Device

An important treatment element when considering injectable treatment therapy is the device that delivers the medication. Research has demonstrated that improvements in injection delivery systems have a positive outcome in terms of patients' treatment acceptability, satisfaction, and convenience and may help decrease social stigma associated with injection therapy (34–38). Tirzepatide is administered with a single-dose pen and uses the same injection device that is used to administer dulaglutide. In a study that evaluated the safe and effective use of the dulaglutide single-dose pen, most patients (99%) found the device "easy" or "very easy" to use (39). Similarly, although no study has been conducted to assess patient preference for the tirzepatide pen, there has been research on the same device published in the literature. In the crossover PREFER study, injection-naive participants with type 2 diabetes preferred the single-dose pen to the semaglutide pen (84.2 vs. 12.3%) (40). More participants found the single-dose pen easier to use (86.8 vs. 6.8%) and were willing to use it compared with the semaglutide pen (93.5 vs. 45.8%). Shorter training time was required for participants to learn to use the single-dose pen device versus the semaglutide device (3.38 vs. 8.14 minutes). Because no active drug was administered directly into patients in this study and the device procedures are not affected by the drug dosage, these findings could be extrapolated to anticipate the patient preference between the tirzepatide pen and the semaglutide pen. Therefore, given the consistency of the single-use pen device across dulaglutide and tirzepatide and across doses, patients' perceptions regarding device ease of use and preferences should remain the same (39,40).

Patient preferences are an important element of patient-centered care, the provision of which is essential to effective diabetes management and a cornerstone of diabetes treatment guidelines around the world. Past ADA/European Association for the Study of Diabetes guidelines have noted that, "Even in cases where clinical characteristics suggest the use of a particular medication based on the available evidence from clinical trials, patient preferences regarding route of administration, injection devices, side effects, or cost may prevent their use by some individuals" (1). Thus, ease of use and patient preference of medical devices should be considered when physicians are evaluating different therapeutic options for their patients.

Clinical Implications for the Use of Tirzepatide in Primary Care

Based on the clinically and statistically significant A1C reduction and weight loss with low risk of hypoglycemia versus comparators, tirzepatide can be regarded as a potential treatment choice for a broad spectrum of patients with type 2 diabetes. With current treatment, normoglycemia (A1C <5.7%) without an increased risk of hypoglycemia has not been considered attainable. The SURPASS program included patient populations that are representative of the type 2 diabetes treatment continuum observed in clinical practice, although because of the global nature of the SURPASS program, the data might not be representative of local demographics.

The range of background antihyperglycemic medications included in the SURPASS program covers relevant oral (metformin, SGLT2 inhibitors, and sulfonylureas) and injectable (basal insulins) antidiabetic drugs commonly used in primary care. The addition of tirzepatide to a basal insulin (SURPASS-5) resulted in improved glycemic control and weight loss without an increased risk of hypoglycemia and reduction in insulin dosage. It is anticipated that a more stringent insulin down-titration may result in substantial insulin sparing while maintaining glycemic control and potentially reducing hypoglycemia risk.

The choice of active comparators and dosing in the SURPASS trials has been driven by the importance these agents have and will have in clinical care. For example, semaglutide 1 mg (used in SURPASS-2) was considered a potent GLP-1 receptor agonist available on the market at the time the study was conducted (41,42). On the other hand, basal insulins degludec and glargine are widely prescribed in patient populations inadequately controlled on oral antihyperglycemic medications and followed an adequate dose titration as demonstrated by the glycemic efficacy results achieved in SURPASS-3 and SURPASS-4, respectively (24,25).

The AE profile of tirzepatide is similar to that of the GLP-1 receptor agonists. Although GI AEs were the most commonly observed AEs with tirzepatide, they affected a minority of patients with mild to moderate severity and tended to occur during treatment initiation. GI AEs can be managed with mitigating measures such as eating smaller and more frequent meals throughout the day, stopping eating when feeling full, or taking prescribed symptomatic medications per physician advice. Patients should be informed that GI AEs generally dissipate over time.

It must be noted that the durations of the completed SURPASS trials were 40 to 52 weeks, although the efficacy and safety of tirzepatide has been shown to be sustained for up to 2 years in ∼10% of participants in SURPASS-4. In any case, longer-term and real-world data will be necessary for an enhanced understanding of the clinical profile of tirzepatide in primary care.

Based on pharmacokinetic studies of tirzepatide in people with varying degrees of renal or hepatic impairment, no dose adjustment is anticipated in this patient population (43,44).

Finally, a ready-to-use single-dose pen can help to make treatment with tirzepatide an attractive option for patients with type 2 diabetes who are naive to self-injection or injecting others (39). All these factors need to be considered by clinicians in combination with the drug's efficacy, safety, and other important treatment attributes.

Conclusion

Tirzepatide offers primary care providers and patients a first-in-class option to treat a wide spectrum of type 2 diabetes by achieving significant reductions in A1C (ranging from −1.87 to −2.59%) while also achieving substantial weight loss (ranging from −6.6 to −13.9%) and maintaining a low risk of hypoglycemia. The safety profile of tirzepatide is similar to that of GLP-1 receptor agonists, with GI side effects being the most common AEs. These GI AEs are transient and mild to moderate in severity, and their frequency decreases over time.

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AUTHOR CONTRIBUTIONS

P.K., J.E.A., J.S., K.S.B., K.R., and J.A.L. interpreted the data and critically revised the manuscript for important intellectual content. K.S.B., K.R., A.T.-G., and J.A.L. contributed to the conception of the article. K.S.B., A.T.-G., and J.A.L. researched data and wrote the manuscript. All of the authors approved of this manuscript to be submitted for publication. J.A.L. is the guarantor of this work and, as such, had full access to all the data reported and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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