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Real-world use and effectiveness of tirzepatide among individuals without type 2 diabetes: Results from the Optum Market Clarity database

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Abstract

Aims: To understand real-world tirzepatide utilization and effectiveness (change in weight and body mass index [BMI]) among people without type 2 diabetes (T2D) in the United States.

Materials and Methods: This retrospective, observational study used Optum's de-identified Market Clarity database (index date: first-observed tirzepatide claim; index period: 13 May 2022–30 September 2023). Outcomes were assessed in 3 cohorts: (1) Overall cohort: age ≥18 years; ≥1 tirzepatide claim; no baseline T2D diagnosis codes, anti-diabetes medication use (except metformin) or glycated haemoglobin ≥6.5%; continuous medical and pharmacy enrolment for ≥12 months pre-index. (2) Utilization cohort: all above criteria and anti-obesity medication (AOM)-eligible individuals (BMI ≥30 kg/m^2, or ≥27 kg/m^2 with ≥1 obesity-related complication [ORC]) for assessment of tirzepatide utilization (persistence, discontinuation, dose escalation and switching 6 months post-index). (3) Effectiveness cohort: all above criteria and AOM-eligible glucagon-like peptide-1 receptor agonist (GLP-1 RA)-naive individuals persistent on tirzepatide for ≥6 months with pre- and post-index weight and BMI measurements for assessment of tirzepatide effectiveness (mean absolute and percent bodyweight/BMI change from baseline and bodyweight/BMI reduction ≥5%, ≥10%, ≥15% and ≥20%). All analyses were descriptive.

Results: Overall cohort included 20,998 individuals (mean age: 47.4 years, female: 74.9%, mean BMI: 36.9 kg/m^2). At index, 66.0% of individuals had ≥1 ORC, while 44.4% had ≥2 ORCs. Persistence in the utilization cohort was 55.4%; 30.8% switched to a different AOM/GLP-1 RA analogue or restarted tirzepatide after discontinuation, and by the sixth prescription fill, 74.2% were on <10 mg tirzepatide. Mean weight

reduction in the effectiveness cohort was 11.9% at 6 months post-index (≥5%: 85.8%; ≥10%: 61.5%).

Conclusions: Real-world evidence suggests multimorbidity is common among tirzepatide initiators. While tirzepatide dose escalation was slower than in clinical trials, individuals achieved weight reduction at 6 months, consistent with clinical trials.

KEYWORDS
anti-obesity medications, obesity, treatment patterns, tirzepatide

1 | INTRODUCTION

In the United States (US), the prevalence of obesity increased from 30.5% in 2000 to 41.9% in 2020 and is estimated to reach 50% by 2030.[1–3] The estimated annual medical cost of treating obesity in the US was $173 billion in 2019.[4] Obesity and obesity-related complications such as type 2 diabetes (T2D), cardiovascular diseases and mental health-related conditions impose a substantial economic burden on people and healthcare systems and are major contributors to global morbidity and mortality.[5,6] The American Heart Association predicted that by 2050, the prevalence of established diseases in the US will reach 60.6% for obesity, 26.8% for T2D and 15.0% for total cardiovascular disease.[7] Current treatment guidelines for obesity recommend the use of anti-obesity medications (AOMs) as an adjunct to lifestyle interventions to promote weight reduction and for the prevention and resolution of obesity-related complications.[8–10] For people with obesity, 5%–10% weight reduction can be clinically meaningful and potentially reduces the likelihood of developing T2D while improving cardiometabolic risk factors and some associated obesity-related complications.[9,11,12]

Tirzepatide is a once weekly glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist (RA) approved in the US for the treatment of T2D in May 2022, for obesity in November 2023 and for obstructive sleep apnea in December 2024.[13–15] In the phase 3 SURMOUNT clinical trials, treatment with tirzepatide resulted in clinically meaningful mean bodyweight reduction in adults with obesity (body mass index [BMI] ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2 and at least one obesity-related complication excluding T2D).[16–18] In SURMOUNT-1 (NCT04184622), 72 weeks of tirzepatide (15 mg) treatment led to a mean weight reduction of 22.5% (efficacy estimand).[17] SURMOUNT-3 (NCT04657016) demonstrated that after treatment with the maximum tolerated dose (MTD) of tirzepatide (10 or 15 mg), participants achieved a total mean weight reduction of 26.6% over 84 weeks (12 weeks of intensive lifestyle intervention, followed by a 72-week treatment period; efficacy estimand).[18] In SURMOUNT-4 (NCT04660643), participants achieved a mean weight reduction of 20.9% during the tirzepatide MTD lead-in period (36 weeks); participants continuing tirzepatide MTD for 52 weeks experienced an additional 6.7% weight reduction, whereas those who switched to placebo experienced a 14.8% weight regain (efficacy estimand).[16] Tirzepatide significantly reduced obstructive sleep apnea severity relative to placebo in phase 3 randomized clinical trials.[19] Among adults with heart failure with preserved ejection fraction and obesity, tirzepatide demonstrated a 38% reduction in the relative risk of time-to-first occurrence of adjudicated death from cardiovascular causes or a worsening heart failure event compared with placebo (hazard ratio: 0.62; 95% confidence interval [CI]: 0.41 to 0.95; $p = 0.026$) in the SUMMIT trial.[20] Tirzepatide is also under investigation for reduction of morbidity and mortality in adults living with obesity (SURMOUNT-MMO; NCT05556512).[21]

Real-world evidence on the use and effectiveness of tirzepatide is limited. The current study aimed to understand the real-world use of tirzepatide among people without T2D in the Optum Market Clarity database, including baseline characteristics, tirzepatide utilisation and tirzepatide effectiveness.

2 | METHODS

2.1 | Study design and data source

This was a retrospective, observational study conducted in the US using de-identified patient health information from the Optum Market Clarity database. The de-identified Optum Market Clarity database deterministically links medical and pharmacy claims with electronic health record data for over 75 million individuals from providers across the continuum of care.[22] Refer to Supplementary methods for code identification.

The de-identified data were fully compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996. Given the use of retrospective and de-identified data, the study did not require Institutional Review Board approval. This study was conducted in accordance with the ethical principles as stated in the Declaration of Helsinki and consistent with Good Pharmacoepidemiology Practices and the applicable laws and regulations of the US.

2.2 | Study population

The study included individuals with at least one pharmacy claim for tirzepatide during the index period (13 May 2022–30 September 2023). The first-observed claim of tirzepatide was designated as the

index date. Eligible individuals were adults ≥18 years with ≥1 pharmacy claim for tirzepatide, without T2D (no baseline T2D diagnosis codes or glycated haemoglobin [HbA1c] ≥6.5% and no anti-diabetes medication use [except metformin], during the pre-index period [baseline] inclusive of the index date); and with continuous medical and pharmacy enrolment for at least 12 months pre-index with no more than a 30-day gap (Supplementary Figures S1 and S2). Metformin use was allowed as it may have been prescribed for other conditions, such as polycystic ovarian syndrome. Individuals with complications associated with unintentional weight change during the study period were excluded (Supplementary Table S1). During the index period, tirzepatide was only approved for the treatment of T2D; therefore, any use of tirzepatide by individuals without T2D during this time was off-label and solely at the discretion of their prescribing physician.

The study population was grouped into 3 nested cohorts: (1) Overall cohort: Individuals meeting the inclusion criteria. (2) Utilization cohort: Individuals meeting the inclusion criteria and who were eligible for use of AOMs (BMI as noted in the electronic health record: ≥30 kg/m^2 or ≥27 kg/m^2 with ≥1 obesity-related complication) and continuously enrolled for 6 months post-index. (3) Effectiveness cohort: meeting all above inclusion criteria and AOM-eligible individuals who were GLP-1 RA-naive (i.e., had never received GLP-1 RAs including dulaglutide, liraglutide and insulin degludec, lixisenatide, exenatide microspheres, exenatide, semaglutide, liraglutide, or lixisenatide and insulin glargine [excluding tirzepatide]) pre-index, were persistent on tirzepatide for at least 6 months post-index (defined as no more than 60-day gap), and had weight and BMI measurements available in the electronic health records at baseline and at 6 months post-index. As the utilization and effectiveness cohorts were subgroups of the overall cohort, an individual could be included in more than one cohort in this study.

2.3 | Study outcomes

2.3.1 | Demographic and clinical characteristics

Demographic characteristics at the index date included age, sex, race, ethnicity, payer type and prescribing healthcare provider specialty. Clinical and treatment pattern characteristics during the 12-month pre-index period (inclusive of the index date) included BMI and obesity class, weight, obesity-related complications (Supplementary Table S1) and prior obesity treatments (AOMs, lifestyle interventions [including behavioural counselling, weight management classes, medical nutrition therapy, nutrition classes and nutritional counselling, dietitian visit], and bariatric surgery).

2.3.2 | Tirzepatide utilization

Tirzepatide utilization, including persistence, discontinuation, dose escalation and switching, was assessed during the 6-month post-index period in the utilization cohort. Persistence was assessed during two time periods: 13 May 2022–31 December 2022 from an earlier analysis (inclusion criteria were identical as the current analysis except: HbA1c ≥6.5% was not an exclusion criterion, and absence of baseline T2D diagnosis codes was exclusive of the index date),[23] and 13 May 2022–30 September 2023 from the current analysis. Individuals were considered persistent if they had not discontinued tirzepatide, and discontinuation was defined as a failure to refill tirzepatide within 60 days after depletion of the previous days' supply (60-day gap); a sensitivity analysis with a 45-day gap was also conducted. For measures of persistence, stockpiling was not considered, so days from overlapping fills did not contribute to the days' supply. A sensitivity analysis with stockpiling enabled for tirzepatide prescription was also conducted (45-day gap and 60-day gap) so that days from overlapping fills contributed to days' supply. Time to discontinuation and tirzepatide dose at discontinuation were assessed. Dose distributions (proportion of individuals filling 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg or 15 mg) from index to sixth tirzepatide fill were reported. The proportion of individuals switching, defined as the presence of at least one prescription for any of the previously listed AOMs or GLP-1 RA analogues (excluding tirzepatide) from the date of discontinuation (60-day gap) until the end of the 6-month post-index period, was assessed. Tirzepatide re-initiation after discontinuation (60-day gap) was defined as the presence of at least one tirzepatide prescription fill from the date of discontinuation until the end of the 6-month post-index period.

2.3.3 | Tirzepatide effectiveness

Tirzepatide effectiveness was assessed at 6 months post-index in the effectiveness cohort among individuals with pre- and post-index measurements; weight and BMI closest to the index date and 6 months post-index or the closest record available 5–7 months post-index were reported. Changes from baseline in weight and BMI (absolute and percent) and the proportion of individuals achieving weight and BMI reduction targets of ≥5%, ≥10%, ≥15% and ≥20% at 6 months post-index were reported.

2.4 | Statistical analyses

Statistical analyses were conducted using the Instant Health Data tool. Descriptive statistics presented categorical variables as frequencies and percentages, and continuous variables as means and standard deviations (SDs) or medians and interquartile ranges (IQR). The proportion of individuals with missing data was reported with no imputation of missing values.

3 | RESULTS

This study included 20,998 individuals without a diagnosis of T2D or HbA1c ≥6.5% and no use of anti-diabetes medications (except metformin) who initiated tirzepatide during the index period; these individuals comprised the 'overall cohort' (Table 1). Of these, 3459 individuals comprised the 'utilization cohort'. A total of 239 individuals in the utilization cohort were GLP-1 RA-naive, persistent on

TABLE 1 Baseline demographic and clinical measures in tirzepatide initiators.

	Overall $N = 20\,998$	Utilization $n = 3459$	Effectiveness $n = 239$
Baseline characteristics at index			
Age, years, mean (SD)	47.4 (11.5)	47.2 (11.2)	49.5 (10.8)
Sex			
Female	15 733 (74.9)	2614 (75.6)	189 (79.1)
Race			
Asian	198 (0.9)	17 (0.5)	–
Black	1739 (8.3)	317 (9.2)	28 (11.7)
Caucasian	16 913 (80.6)	2882 (83.3)	196 (82.0)
Missing	2148 (10.2)	243 (7.0)	15 (6.3)
Ethnicity			
Hispanic	894 (4.3)	135 (3.9)	15 (6.3)
Not Hispanic	17 020 (81.1)	2928 (84.7)	191 (79.9)
Missing	3084 (14.7)	396 (11.5)	33 (13.8)
Payer at index			
Commercial	18 872 (89.9)	3192 (92.3)	224 (93.7)
Medicaid	986 (4.7)	137 (4.0)	5 (2.1)
Medicare/Medicare advantage	1001 (4.8)	116 (3.4)	10 (4.2)
Other/missing/unknown	139 (0.7)	14 (0.4)	–
Prescribing provider specialty			
Primary care physician	15 873 (81.0)	2685 (82.7)	191 (83.8)
Endocrinologist	692 (3.5)	129 (4.0)	19 (8.3)
Obstetrician/gynaecologist	507 (2.6)	104 (3.2)	2 (0.9)
Gastroenterology	82 (0.4)	15 (0.5)	–
Others	2015 (10.3)	263 (8.1)	13 (5.7)
Unknown	433 (2.2)	52 (1.6)	3 (1.3)
Clinical characteristics[a]			
BMI[b], kg/m^2	**$n = 5437$**	**$n = 3459$**	**$n = 239$**
Mean (SD)	36.9 (8.0)	38.1 (7.6)	38.9 (8.0)
BMI category	**$n = 5437$**	**$n = 3459$**	**$n = 239$**
Overweight: 25- < 30 kg/m^2	783 (14.4)	249 (7.2)	16 (6.7)
Class 1 obesity: 30- < 35 kg/m^2	1488 (27.4)	1044 (30.2)	57 (23.9)
Class 2 obesity: 35- < 40 kg/m^2	1311 (24.1)	903 (26.1)	72 (30.1)
Class 3 obesity: ≥40 kg/m^2	1745 (32.1)	1263 (36.5)	94 (39.3)
Normal weight or lower: <25 kg/m^2	110 (2.0)	–	–
Weight[c], lbs	**$n = 5465$**	**$n = 3458$**	**$n = 239$**
Mean (SD)	230.6 (57.9)	238.9 (55.2)	242.7 (61.5)
HbA1c[d], %	**$n = 394$**	**$n = 242$**	**$n = 60$**
Mean (SD)	5.6 (0.4)	5.7 (0.4)	5.7 (0.4)
Prior obesity treatments			
AOM prescription	2435 (11.6)	434 (12.6)	3 (1.3)
Semaglutide (Wegovy®)	1828 (8.7)	311 (9.0)	0
Liraglutide (Saxenda®)	599 (2.9)	128 (3.7)	0
Naltrexone-bupropion (Contrave®)	199 (0.9)	38 (1.1)	1 (33.3)
Phentermine-topiramate (Qsymia®)	80 (0.4)	19 (0.5)	2 (66.7)
Bariatric surgery	26 (0.1)	5 (0.1)	0

(Continues)

TABLE 1 (Continued)

	Overall $N = 20\,998$	Utilization $n = 3459$	Effectiveness $n = 239$
Lifestyle intervention[e]	631 (3.0)	127 (3.7)	7 (2.9)
Metformin prescription	2587 (12.3)	417 (12.1)	33 (13.8)

Note: Values are *n* (%) unless otherwise specified. Cohort definitions: Overall cohort: Adults (≥18 years) without T2D diagnosis, HbA1c ≥6.5% and no use of anti-diabetes medications (except metformin) during the pre-index period. Utilization cohort: Adults (≥18 years) without T2D diagnosis, HbA1c ≥6.5% and no use of anti-diabetes medications (except metformin) who met the AOM eligibility criteria and had continuous 6-month post-index enrolment. Effectiveness cohort: Adults (≥18 years) without T2D diagnosis, HbA1c ≥6.5% and no use of anti-diabetes medications (except metformin) who met the AOM eligibility criteria were GLP-1 RA-naive, were persistent on tirzepatide for ≥6 months, and had weight and BMI measurements available at baseline and at 6 months post-index.

Abbreviations: AOM, anti-obesity medication; BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; N, total number of participants; n, number of participants; ORC, obesity-related complication; SD, standard deviation; T2D, type 2 diabetes.

[a]Clinical characteristics were assessed in the 12-month pre-index period, including the index date.

[b]Most recent BMI measured in the 12-month pre-index period (including the index date).

[c]Most recent weight measured in the 12-month pre-index period (including the index date).

[d]Most recent HbA1c at 1-month pre-index.

[e]Lifestyle interventions included behavioural counselling, weight management classes, medical nutrition therapy, nutrition classes and nutritional counselling, or dietitian visit.

tirzepatide for ≥6 months, and had weight and BMI measurements available at baseline and at 6 months post-index, and comprised the 'effectiveness cohort' (Table 1).

3.1 | Overall demographic and clinical characteristics

The mean (SD) age in the overall cohort was 47.4 (11.5) years; the majority were female (74.9%), Caucasian (80.6%), commercially insured (89.9%), and prescribed tirzepatide by a primary care physician (81.0%; Table 1). Mean (SD) BMI and weight at baseline were 36.9 (8.0) kg/m^2 ($n = 5437$) and 230.6 (57.9) lbs ($n = 5465$), respectively; mean (SD) HbA1c was 5.6% (0.4) ($n = 394$). Most individuals (83.6%) had BMI ≥30 kg/m^2; 27.4% had class 1 obesity (30–<35 kg/m^2); 24.1% had class 2 obesity (35–<40 kg/m^2); 32.1% had class 3 obesity (≥40 kg/m^2). At baseline, 66.0% of individuals had at least one obesity-related complication, while 44.4% had 2 or more obesity-related complications (2: 17.5%; 3: 13.3%; ≥4: 13.6%; Table 2). Hypertension was the most prevalent obesity-related complication (34.5%), followed by dyslipidemia (31.9%) and anxiety (21.8%).

Prior AOM prescriptions were reported for 11.6% of individuals in the overall cohort (Table 1). Semaglutide (8.7%) and liraglutide (2.9%) were the most frequently prescribed AOMs, followed by naltrexone/bupropion (0.9%) and phentermine-topiramate (0.4%). Very few people had previously received lifestyle intervention (3.0%) or bariatric surgery (0.1%).

3.2 | Utilization patterns of tirzepatide

3.2.1 | Cohort characteristics

Baseline demographic characteristics of the utilization cohort ($n = 3459$) were consistent with the overall cohort (mean [SD] age: 47.2 [11.2] years; female: 75.6%; Caucasian: 83.3%; Table 1). Mean (SD) baseline BMI and weight were numerically higher than those of the overall cohort (BMI: 38.1 [7.6] kg/m^2; weight: 238.9 [55.2] lbs). Most individuals (92.8%) had a baseline BMI ≥30 kg/m^2; 77.3% had at least one; and 53.5% had 2 or more obesity-related complications (2: 20.6%; 3: 15.8%; ≥4: 17.0%; Table 2). Like the overall cohort, semaglutide (9.0%) and liraglutide (3.7%) were the most frequently prescribed AOMs; hypertension (40.4%) and dyslipidemia (36.4%) were the two most prevalent obesity-related complications. However, prediabetes (27.6%) was the third most prevalent obesity-related complication in the utilization cohort, unlike anxiety in the overall cohort.

3.2.2 | Tirzepatide utilization patterns

Most individuals in the utilization cohort (90.3%) initiated tirzepatide on doses of 2.5 mg or 5 mg at the index date (Supplementary Figure S1). A total of 60.5% and 53.0% of individuals had 5 and 6 tirzepatide prescription refills, respectively. The most common dose at the sixth prescription fill was 5 mg (33.0%); 25.8% of individuals were receiving a 10 mg dose of tirzepatide or higher (Supplementary Figure S3).

In the initial analysis (13 May 2022–31 December 2022),[23] more than two-thirds of the cohort (68.1%) was persistent (60-day gap); the median (IQR) time to discontinuation among individuals who discontinued tirzepatide was 56 (27–88) days (Table 3). When a 45-day gap was considered, 63.5% of people were persistent. In the current analysis (13 May 2022–30 September 2023), more than half of the utilization cohort (55.4%) was persistent (60-day gap); the median (IQR) time to discontinuation was 40 (27–77) days. When a 45-day gap was considered, 51.3% of people were persistent, with a median (IQR) time to discontinuation of 46 (27–83) days. In the sensitivity analysis, when stockpiling was accounted for, 70.6% of individuals remained persistent (45-day gap), while 71.9% remained persistent during the 60-day gap (Table 3).

At the time of discontinuation, most individuals were receiving either 2.5 mg (42.5%) or 5 mg (37.5%) of tirzepatide (Table 3). Among individuals who discontinued tirzepatide (60-day gap), 30.8% switched

TABLE 2 Presence of obesity-related complications during pre-index period.

	Overall $N = 20\,998$	Utilization $n = 3459$	Effectiveness $n = 239$
At least 1 ORC, *n* (%)	13 858 (66.0)	2675 (77.3)	198 (82.9%)
Number of ORCs, *n* (%)			
0	7140 (34.0)	784 (22.7)	41 (17.2%)
1	4545 (21.6)	825 (23.9)	61 (25.5%)
2	3676 (17.5)	714 (20.6)	53 (22.2%)
3	2791 (13.3)	548 (15.8)	37 (15.5%)
4+	2846 (13.6)	588 (17.0)	47 (19.7%)
ORCs, *n* (%)			
Hypertension	7235 (34.5)	1396 (40.4)	107 (44.8)
Dyslipidemia	6701 (31.9)	1258 (36.4)	99 (41.4)
Anxiety	4581 (21.8)	813 (23.5)	50 (20.9)
Prediabetes	4420 (21.1)	954 (27.6)	76 (31.8)
Gastroesophageal reflux disease	3341 (15.9)	703 (20.3)	43 (18.0)
Obstructive sleep apnea	2987 (14.2)	604 (17.5)	53 (22.2)
Male hypogonadism	692 (13.2)	117 (13.9)	8 (16.0)
Asthma or reactive airway disease	1798 (8.6)	338 (9.8)	22 (9.2)
Depression	1721 (8.2)	297 (8.6)	16 (6.7)
Osteoarthritis	1671 (8.0)	346 (10.0)	22 (9.2)
Osteoarthritis of knee	1411 (6.7)	295 (8.5)	19 (8.0)
Metabolic syndrome	1256 (6.0)	264 (7.6)	21 (8.8)
Cardiovascular disease	1212 (5.8)	226 (6.5)	16 (6.7)
Polycystic ovary syndrome	700 (4.5)	135 (5.2)	8 (4.2)
Metabolic dysfunction-associated steatohepatitis or metabolic dysfunction-associated steatotic liver disease	861 (4.1)	161 (4.7)	12 (5.0)
Urinary incontinence	457 (2.2)	86 (2.5)	10 (4.2)
Cerebrovascular disease	272 (1.3)	43 (1.2)	0
Congestive heart failure	241 (1.2)	50 (1.5)	3 (1.3)
Peripheral vascular disease	184 (0.9)	28 (0.8)	4 (1.7)
Female infertility	75 (0.5)	15 (0.6)	1 (0.5)
Myocardial infarction	61 (0.3)	13 (0.4)	1 (0.4)

Note: Cohort definitions: Overall cohort: Adults (≥18 years) without T2D diagnosis, HbA1c ≥6.5% and no use of anti-diabetes medications (except metformin) during the pre-index period. Utilization cohort: Adults (≥18 years) without T2D diagnosis, HbA1c ≥6.5% and no use of anti-diabetes medications (except metformin) who met the AOM eligibility criteria and had continuous 6-month post-index enrolment. Effectiveness cohort: Adults (≥18 years) without T2D diagnosis, HbA1c ≥6.5% and no use of anti-diabetes medications (except metformin) who met the AOM eligibility criteria were GLP-1 RA- naive, were persistent on tirzepatide for ≥6 months, and had weight and BMI measurements available at baseline and at 6 months post-index.
Abbreviations: AOM, anti-obesity medication; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; ORC, obesity-related complication; T2D, type 2 diabetes.

to a different AOM or GLP-1 RA analogue or restarted tirzepatide after discontinuation during the 6-month post-index period.

3.3 | Tirzepatide effectiveness: change in weight and BMI

3.3.1 | Cohort characteristics

Demographic characteristics of the effectiveness cohort ($n = 239$) were consistent with the overall and utilization cohorts (mean [SD] age: 49.5 [10.8] years; female: 79.1%; Caucasian: 82.0%; Table 1), with some notable differences in clinical characteristics. Mean (SD) BMI and weight at baseline were similar to the utilization cohort and numerically higher than the overall cohort (38.9 [8.0] kg/m^2 and 242.7 [61.5] lbs, respectively). Overall, 93.3% of individuals in the effectiveness cohort had a BMI ≥30 kg/m^2; 82.9% had at least one and 57.3% reported 2 or more obesity-related complications (2: 22.2%; 3: 15.5%; ≥4: 19.7%; Table 2). Like the utilization cohort, the most prevalent obesity-related complications were hypertension (44.8%), dyslipidemia (41.4%) and prediabetes (31.8%).

TABLE 3 Tirzepatide utilization in AOM-eligible individuals (6-month post-index period).

	Utilization	
	Stockpiling disabled	Stockpiling enabled
Time period: 13 May 2022–31 December 2022	***n* = 1117***	
Persistence (45-day gap), *n* (%)	709 (63.5)	
Discontinuation, *n* (%)	408 (36.5)	
Time to discontinuation, days, median (IQR)	59.5 (27–95.3)	
Time to discontinuation, days, min-max	27–138	
Persistence (60-day gap), *n* (%)	761 (68.1)	
Discontinuation, *n* (%)	356 (31.9)	
Time to discontinuation, days, median (IQR)	56 (27–88)	
Time to discontinuation, days, min-max	27–121	
Time period: 13 May 2022–30 September 2023	***n* = 3459**	
Persistence (45-day gap), *n* (%)	1773 (51.3)	2441 (70.6)
Discontinuation, *n* (%)	1686 (48.7)	1018 (29.4)
Time to discontinuation, days, median (IQR)	46 (27–83)	55 (27–84)
Time to discontinuation, days, min-max	0–138	0–135
Discontinuation dose		
2.5 mg	434 (39.6)	205 (43.1)
5 mg	411 (37.5)	178 (37.4)
7.5 mg	140 (12.8)	56 (11.7)
10 mg	73 (6.7)	23 (4.8)
12.5 mg	24 (2.2)	8 (1.7)
15 mg	14 (1.3)	6 (1.3)
Post discontinuation treatment	*n* = 1686	*n* = 1018
Switch to different AOM or GLP-1 RA analogue or restart tirzepatide	558 (33.1)	308 (30.3)
Switch to different AOM post discontinuation	197 (11.7)	112 (11.0)
Switch to different AOM or GLP-1 RA analogue post discontinuation	318 (18.9)	183 (18.0)
Restart tirzepatide post discontinuation up to 6 months post-index	240 (14.2)	125 (12.3)
Persistence (60-day gap)	1916 (55.4)	2486 (71.9)
Discontinuation	1543 (44.6)	973 (28.1)
Time to discontinuation, days, median (IQR)	40 (27–77)	55 (27–83)
Time to discontinuation, days, min-max	0–121	0–121
Discontinuation dose		
2.5 mg	413 (42.5)	201 (44.6)
5 mg	365 (37.5)	170 (37.7)
7.5 mg	110 (11.3)	49 (10.9)
10 mg	58 (6.0)	21 (4.7)
12.5 mg	18 (1.9)	6 (1.3)
15 mg	9 (0.9)	4 (0.9)
Post discontinuation treatment	*n* = 1543	*n* = 973
Switch to different AOM or GLP-1 RA analogue or restart tirzepatide	475 (30.8)	269 (27.7)
Switch to different AOM post discontinuation	189 (12.2)	111 (11.4)
Switch to different AOM or GLP-1 RA analogue post discontinuation	309 (20.0)	182 (18.7)
Restart tirzepatide post discontinuation up to 6 months post-index	166 (10.8)	87 (8.9)

Note: AOMs or GLP-1 RA analogues include dulaglutide, liraglutide and insulin degludec, lixisenatide, exenatide microspheres, exenatide, semaglutide, liraglutide, or lixisenatide and insulin glargine. Stockpiling disabled: Days from overlapping fills did not contribute to days' supply. Stockpiling enabled: Days from overlapping fills contributed to days' supply. 45-day/60-day: a 45- or 60-day allowable gap in days supply before someone is considered to have discontinued. Utilization cohort: Adults (≥18 years) without T2D diagnosis, HbA1c ≥6.5% and no use of anti-diabetes medications (except metformin) who met the AOM eligibility criteria and had continuous 6-month post-index enrolment. Values are *n* (%) unless otherwise specified. * For this population, HbA1c ≥6.5% was not an exclusion criterion and absence of baseline T2D diagnosis codes was exclusive of the index date.[23]

Abbreviations: AOM, anti-obesity medication; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; PDC, proportion of days covered; SD, standard deviation; T2D, type 2 diabetes; IQR, interquartile range.

3.3.2 | Effectiveness

From the mean baseline weight of 242.7 lbs, individuals in the effectiveness cohort achieved a mean (SD) weight reduction of 27.7 (16.7) lbs at 6 months, equivalent to 11.9% reduction (Table 4). Similarly, from the mean baseline BMI of 38.9 kg/m^2, individuals achieved a mean (SD) BMI reduction of 4.5 (2.7) kg/m^2, equivalent to 11.8% reduction. At 6 months post-index, 85.8%, 61.5%, 31.0% and 10.5% of individuals achieved a weight reduction of ≥5%, ≥10%, ≥15% and ≥20%, respectively (Figure 1).

4 | DISCUSSION

This real-world, observational study utilized the Optum Market Clarity claims database to understand the use of tirzepatide in individuals without T2D. The baseline clinical characteristics of individuals initiating tirzepatide in the current study were consistent with those previously reported in the SURMOUNT-1 study.[17] Several tirzepatide initiators had class 2 or class 3 obesity. Depending on the time period, whether stockpiling was considered, and the allowable gap, persistence ranged from 51.3% to 71.9% among individuals in the utilization cohort. The majority of individuals in the effectiveness cohort demonstrated clinically meaningful weight reduction at 6 months post-index.

In a study based on the National Health and Nutrition Examination Survey (2001–2018) in the US, 15.3% of people with obesity were reported to have class 2 or class 3 obesity and the prevalence of obesity was similar in males and females (approximately 34% and 37%, respectively).[24] By contrast, in the current study, 56.2%–69.4% of individuals initiating tirzepatide had a mean BMI ≥35 kg/m^2 consistent with class 2 and class 3 obesity, and 74.9%–79.1% were female, suggesting that AOM users were more likely to be female and have a high BMI relative to the overall population of people with obesity. Plausible explanations could be that individuals whose BMIs are captured in electronic health records tend to have advanced disease severity,[25,26] self-selection of people seeking AOMs or a tendency among healthcare providers to prescribe AOMs to people with higher BMI. While the imbalance of males and females could impact the generalisability of the persistence and weight reduction findings, it is important to note that women predominate in clinical trials of obesity management medications. These observations are consistent with existing literature, which indicates a higher prevalence of obesity among women compared with men.[27,28] Notably, the mean age of the study population ranged from 47.4 to 49.5 years. This finding is consistent with a recent National Centre for Health Statistics report stating that the overall obesity prevalence was higher among adults aged 40–59 years than among those aged 20–39 or >60 years, possibly attributable to lifestyle changes, decreased physical activity or metabolic changes that occur with aging.[29]

At least approximately two-thirds of the individuals in the current study (overall: 66.0%; utilization: 77.3%; effectiveness: 82.9%) had ≥1 obesity-related complication, and over 44% (overall: 44.4%;

TABLE 4 Tirzepatide effectiveness in AOM-eligible GLP-1 RA-naive individuals persistent on tirzepatide.

	Effectiveness $n = 239$
Baseline BMI, kg/m^2, mean (SD)	38.9 (8.0)
Post-index BMI, kg/m^2, mean (SD)	34.5 (8.4)
BMI reduction from baseline to 6 months post-index	
Absolute reduction, kg/m^2, mean (SD)	4.5 (2.7)
Percent reduction, mean (SD)	11.8 (7.0)
Baseline weight, lbs, mean (SD)	242.7 (61.4)
Post-index weight, lbs, mean (SD)	215.0 (62.2)
Weight reduction from baseline to 6 months post-index	
Absolute reduction, lbs, mean (SD)	27.7 (16.7)
Percent reduction, mean (SD)	11.9 (6.9)

Note: Values are *n* (%) unless otherwise specified. Effectiveness cohort: Adults (≥18 years) without T2D diagnosis, HbA1c ≥6.5% and no use of anti-diabetes medications (except metformin) who met the AOM eligibility criteria were GLP-1 RA-naive, were persistent on tirzepatide for ≥6 months, and had weight and BMI measurements available at baseline and at 6 months post-index.
Abbreviations: AOM, anti-obesity medication; BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; lbs, pounds; SD, standard deviation; T2D, type 2 diabetes.

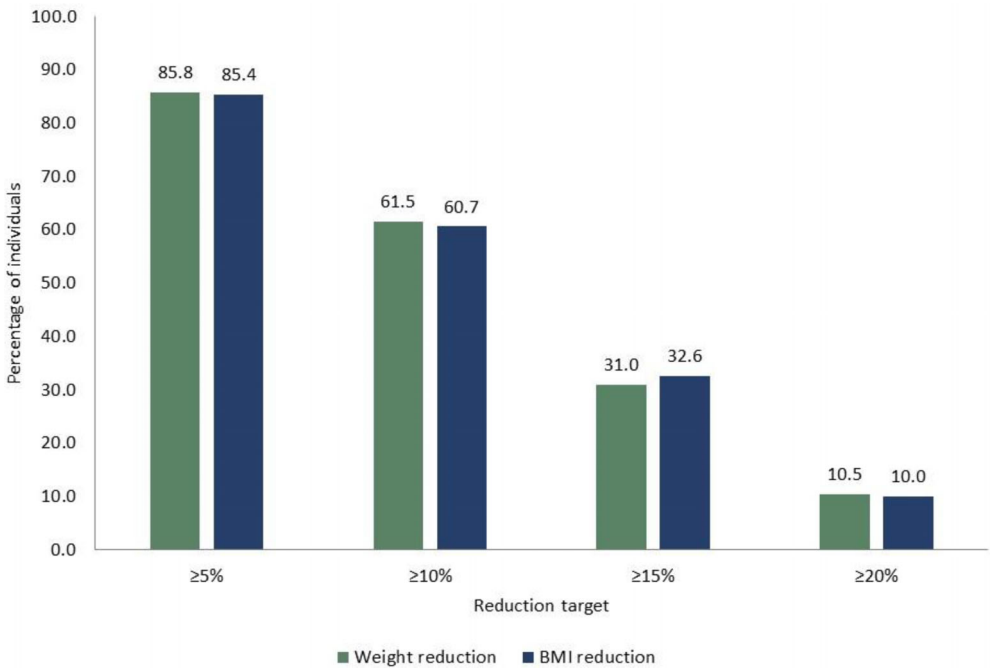

FIGURE 1 Reduction in weight and BMI in AOM-eligible GLP-1 RA-naive individuals persistent on tirzepatide. Effectiveness cohort: Adults (≥18 years) without T2D diagnosis, HbA1c ≥6.5% and no use of anti-diabetes medications (except metformin) who met the AOM eligibility criteria were GLP-1 RA-naive, were persistent on tirzepatide for ≥6 months, and had weight and BMI measurements available at baseline and at 6 months post-index. AOM, anti-obesity medications; BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; T2D, type 2 diabetes.

utilization: 53.4%; effectiveness: 57.3%) had ≥2 obesity-related complications. Previous studies demonstrated that higher weight classes were associated with multiple obesity-related complications, higher healthcare costs and impaired quality of life.[30–32] For example, people with obesity and multimorbidity had significantly higher annual all-cause total costs ($26 624 vs. $24 838; $p < 0.0001$) compared with the normal-weight/overweight cohort,[33] and people with class 2 and class 3 obesity incurred 12%–20% more annual healthcare expenditures than normal-weight individuals.[34]

Prior treatments for obesity across multiple modalities were low in the current study. For example, <13% of individuals had AOM prescriptions during the 12-month pre-index period in the overall or utilization cohorts. Semaglutide and liraglutide were the most frequently prescribed AOMs. Furthermore, about 3% of individuals had previously undergone lifestyle intervention, and 0.1% had undergone bariatric surgery. This low utilization of prior obesity treatments in AOM-eligible individuals could potentially be attributed to multiple factors, including prescriber preferences towards lifestyle modifications as the primary intervention for obesity treatment, societal stigma associated with obesity treatment and insufficient awareness of available treatments.[35–37] Semaglutide's approval for obesity treatment by the US Food and Drug Administration in June 2021 and the use of other GLP-1 RAs for weight management might also explain the low utilization of semaglutide during the study period.[38]

Persistence varied depending on the time period of measurement and whether stockpiling was considered. Persistence (60-day gap) was 55.4% and 68.1%[23] when assessed from 13 May 2022–30 September 2023 and 13 May 2022–31 December 2022, respectively. Persistence was higher (71.9%) when stockpiling was considered. The difference in persistence between the two time periods could potentially be attributed to known supply chain constraints that may have differentially impacted the assessment periods.[39] According to the Academy of Managed Care Pharmacy, individuals stockpile as a precaution against supply chain disruptions, increased demand, lapsing of copay cards or in anticipation of future requirements.[40] Notably, all measures of persistence reported here are higher than the overall persistence (46.3% at 6 months) previously reported for GLP-1 RAs among GLP-1 RA-naive, commercially insured adults with obesity without diabetes.[41] Over 30% of people who discontinued tirzepatide either switched to a different AOM or GLP-1 RA analogue or restarted tirzepatide during the 6-month post-index period. Possible explanations could be access restrictions due to off-label use, supply constraints, treatment barriers such as adverse events or tolerability, or inadequate insurance coverage.

Consistent with tirzepatide dosing recommendations for obesity, the majority of individuals in the utilization cohort were initiated on tirzepatide doses of 2.5 mg or 5 mg at index.[42] However, most people did not escalate up to the MTD (10 mg or 15 mg) as observed in phase 3 clinical trials, and nearly one-third (33.0%) remained on 5 mg of tirzepatide by the sixth prescription fill.[17] This could potentially be attributed to prescribing physicians' preference for lower doses or supply constraints with the higher doses.

A recent real-world study of 343 people with obesity or overweight receiving the maximum maintenance dose of semaglutide (2.4 mg) reported a mean 10.0% bodyweight reduction at 6 months.[43] In the current study, despite most AOM-eligible GLP-1 RA-naive individuals not receiving higher doses of tirzepatide (10 mg or 15 mg) at the sixth refill (approximately 75%), tirzepatide treatment showed a mean weight reduction of 11.9% at 6 months. This is comparable with the mean weight reduction in the phase 3 SURMOUNT-1 trial following 24 weeks of tirzepatide treatment (particularly at the 5 mg dose, which was the most common dose prescribed at the sixth fill in the current study),[17] which is noteworthy considering, unlike the clinical trial, individuals in the current study could have gaps in treatment of up to 60 days, which may impact treatment effectiveness.

In SURMOUNT-1, 85% of participants receiving tirzepatide 5 mg achieved ≥5% bodyweight reduction after 72 weeks.[17] Similarly, in the current study, 85.8% of individuals on low doses of tirzepatide (<10 mg) achieved ≥5% weight reduction as early as 24 weeks. As per the American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for the treatment of people with obesity, a 5%–10% weight reduction is considered to have a clinically meaningful effect on cardiometabolic markers and comorbidities.[9,44–46] For instance, a 5%–15% weight reduction is recommended for people with obesity and prediabetes to prevent T2D, obstructive sleep apnea and hypertension.[47] In recent post hoc analyses of the SURMOUNT-1 trial, tirzepatide treatment was associated with a significant reduction in the 10-year predicted risk of developing T2D and atherosclerotic cardiovascular disease in people with obesity, regardless of baseline glycemic status.[48,49] Over a 176-week treatment period, tirzepatide also significantly reduced the risk of developing T2D compared with placebo by 94% (1.2% vs. 12.6%, respectively; efficacy estimand; hazard ratio: 0.06; 95% CI: 0.03 to 0.13; $p < 0.001$) in SURMOUNT-1 participants with prediabetes.[50] The cardiovascular benefits and impact of tirzepatide on progression to T2D are being investigated in a large, international, phase 3 study in people with obesity or overweight without T2D (SURMOUNT-MMO).[21]

5 | LIMITATIONS

Administrative database analyses have inherent limitations, including potential coding errors, incomplete, inaccurate or missing data and a lack of specific billing codes for some conditions.[51] While available literature provides evidence that weight and BMI data obtained from EHRs can provide valid and efficient measures for estimating treatment effects from randomized controlled trials.[25,52] Specifically, data on body measurements (like weight, height or BMI) might not be consistently or accurately recorded. To address this limitation, we set upper and lower thresholds for BMI (between 9 and 100 kg/m^2) and weight (between 66.1 and 484.2 lbs) to be considered valid for evaluation. This analysis was limited to a US commercially insured, Medicare/Medicare Advantage and Medicaid population, three-quarters of whom were women, which limits the generalizability of the findings. Next, assessing adverse drug reactions is important to comprehensively evaluate medications; however, due to limited data on the most common (i.e., gastrointestinal) adverse events from clinical trials[53] in claims databases, we did not evaluate adverse events. Another

limitation is that tirzepatide samples (2.5 mg) are not captured in claims databases, so possibly more people started on the lowest dose than captured here. Tirzepatide off-label use, supply constraints, access restrictions and copay cards lapsing during the study period may have impacted dose escalation or persistence.[39] Time to discontinuation may have been underestimated as it was reported only among individuals who discontinued tirzepatide. While the current study aimed to understand the real-world use and effectiveness of tirzepatide among people without T2D, due to limited follow-up data, effectiveness could only be assessed among a small proportion of the overall cohort. Finally, potential effects of metformin on metabolic parameters (such as weight) were not separately accounted for or adjusted in the analysis. A more detailed examination of metformin's impact, by either excluding metformin users, conducting subgroup analyses or adjusting for metformin use in statistical models, is an area for future research. Additional research is required to assess the factors that may be predictive of discontinuation, long-term persistence and the effect of tirzepatide on HbA1c levels, weight and long-term clinical outcomes in real-world settings after more follow-up data become available and in the context of discontinuation.

6 | CONCLUSIONS

This real-world retrospective cohort study demonstrated that most people without T2D who initiated tirzepatide had class 2 or class 3 obesity and at least one obesity-related complication, indicating that tirzepatide initiators are progressing in their disease. While dose escalation in the real-world setting was slower than in phase 3 clinical trials and may impact effectiveness, individuals initiating tirzepatide still achieved weight reduction at 6 months consistent with the SURMOUNT-1 trial. These results support the effectiveness of tirzepatide among people with obesity or overweight without T2D.

AUTHOR CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published. All authors were involved in the drafting, critical revision and approval of the final version of the manuscript. Study design and conception: Theresa Hunter Gibble, Jennifer Mary Ward, Emily R. Hankosky, Chanadda Chinthammit. Data collection and analysis: Alexandra Meeks. Interpretation: Ahong Huang, Theresa Hunter Gibble, Donna Mojdami, Emily R. Hankosky, Chanadda Chinthammit.

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CONFLICT OF INTEREST STATEMENT

Emily R. Hankosky, Chanadda Chinthammit, Alexandra Meeks, Jennifer M. Ward, Donna Mojdami and Theresa Hunter Gibble are employees and stockholders of Eli Lilly and Company, Indianapolis, United States. Ahong Huang is a paid consultant of Eli Lilly and Company and has no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The de-identified data were fully compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996. Given the use of retrospective and de-identified data, the study did not require Institutional Review Board approval. This study was conducted in accordance with the ethical principles as stated in the Declaration of Helsinki and consistent with Good Pharmacoepidemiology Practices and the applicable laws and regulations of the US.

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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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