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ORIGINAL ARTICLE

Real world use of tirzepatide in the treatment of type 2 diabetes in an Arab population

Adam Buckley PhD[1] | Sara Suliman PhD[1] | Matthew Allum MD[1] | Nagi Mohammed MD[1] | Nader Lessan MD[1] | Carel W. le Roux PhD[2,3] | Mohamed Suliman MD[1]

[1]Imperial College London Diabetes Centre (ICLDC), Abu Dhabi, UAE

[2]Divisions of Diabetes, Endocrinology and Metabolism, Imperial College London, London, UK

[3]Diabetes Complications Research Centre, Conway Institute, University College Dublin, Dublin, Ireland

Correspondence
Adam Buckley, Imperial College London Diabetes Centre, Abu Dhabi, UAE.
Email: abuckley@icldc.ae

Abstract

Aim: Tirzepatide is a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) dual receptor agonist (RA) that reduces glycated haemoglobin (HbA1c) and weight in patients with type 2 diabetes. We assessed the effectiveness of tirzepatide in real-world use in an Arab population.

Methods: Review of clinical data from a specialist outpatient diabetes centre; study time points and outcome measures were pre-specified.

Results: Tirzepatide was initiated in 8945 patients between 24 October 2022 and 31 December 2023. Of these, 3686 individuals reached 40 weeks of follow-up. At initiation, the mean ± SD age was 54.1 ± 11.5 years, body mass index 34.6 ± 6.0 kg/m^2 and HbA1c 7.3 ± 1.5% (56 ± 17 mmol/mol); 2296 (62%) were switched to tirzepatide from another GLP-RA and 317 (8.6%) reported previous bariatric surgery. The maximum dose dispensed was ≥12.5 mg/week in 1087, 7.5-10.0 mg/week in 1688 and 2.5-5.0 mg/week in 911. The mean 40-week reduction in HbA1c was 0.6 ± 1.2% (8 ± 13 mmol/mol) and the reduction in weight was 4.5 ± 6.9 kg (4.8 ± 7.3%). GLP-RA-naïve patients experienced a significantly greater reduction in HbA1c [1.0 ± 1.3% (11 ± 14 mmol/mol) versus 0.5 ± 1.2% (6 ± 13 mmol/mol), $p < .0001$] and weight (7.2 ± 8.6 vs. 4.2 ± 6.6 kg, $p < .0001$) compared with previously exposed individuals. Post-metabolic bariatric surgery patients lost significantly more weight (7.8 ± 9.4 vs. 4.5 ± 7.0 kg, $p < .0001$). Improvements in blood pressure, lipid profile, and liver transaminases were noted at 40 weeks. Tirzepatide was well tolerated, with 288 (7.8%) of patients discontinuing treatment because of adverse effects, predominantly gastrointestinal.

Conclusion: In real-world use, tirzepatide significantly reduced HbA1c levels and weight and was well tolerated. Previous GLP-RA use was associated with significantly

lesser HbA1c and weight reduction, and previous metabolic bariatric surgery was associated with greater weight loss.

KEYWORDS
glucagon-like peptide-1 receptor agonist, glycaemic control, tirzepatide, type 2 diabetes, weight change

1 | INTRODUCTION

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist (RA). The phase 3 SURPASS programme showed that tirzepatide treatment was effective and safe for patients with type 2 diabetes,[1–5] and it was approved for clinical use in May 2022. The 2022 American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD) consensus report on the management of hyperglycaemia in type 2 diabetes recommended its use as the most effective treatment for HbA1c and weight reduction.[6]

There are no published data on the real-world use of tirzepatide in the treatment of patients with type 2 diabetes to confirm whether the findings seen in randomized controlled trials can be realized in routine clinical practice. The SURPASS studies were largely conducted in GLP-RA-naïve populations and included limited numbers of individuals from the MENA region. We aimed to assess the efficacy and tolerability of tirzepatide in real-world use in an Arab population, and individuals switched from GLP-RA treatment.

2 | RESEARCH DESIGN AND METHODS

Data were collected at the Imperial College London Diabetes Centre (ICLDC), the largest outpatient diabetes facility in the United Arab Emirates. Tirzepatide became available for clinical use in October 2022 with full insurance coverage for all Emirati nationals with type 2 diabetes under the national Thiqa programme and the majority of other patients depending on the insurance plan. ICLDC physicians received education directly from the manufacturer regarding the dose escalation protocol for tirzepatide. The multidisciplinary team at ICLDC includes specialist dieticians and diabetes educators, with access to these services offered at each clinical episode.

The patient database at ICLDC prospectively includes patients who sign a General Consent form for inclusion of anonymized data in research, and was accessed on 1 January 2024 to identify adult individuals dispensed tirzepatide for treatment of type 2 diabetes mellitus since 24 October 2022. The primary outcome was a change in HbA1c, and the secondary outcome was a change in weight at 40 weeks, on an intention-to-treat basis. The cadence of data collection followed ICLDC's clinical diabetes management protocol, with anthropometry performed by trained nurses and HbA1c (Variant II Turbo; Bio-Rad) every 3 months, and lipid profile, renal function and liver enzymes (Cobas 8000; Roche) every 3-6 months as indicated. Follow-up time points of 12, 28 and 40 weeks were chosen to facilitate comparison with the SURPASS studies. As the study used clinical data, we allowed a margin of ±4 weeks around study time points.

We explored tirzepatide treatment outcomes in individuals previously treated with a GLP-RA with a previous history of metabolic bariatric surgery (MBS) in addition to reporting outcomes from the entire study population. Tolerability was assessed by reviewing the electronic clinical records of all patients who discontinued the drug. The study was approved by the ICLDC Research Ethics Committee (ref. IREC081).

2.1 | Statistical analysis

Statistical analysis was performed using R version 4.2.1 (R Foundation for Statistical Computing). Results are presented as mean ± SD or count (%). Parametrically distributed variables were compared using a two-tailed Student's t-test, with paired testing where appropriate. Proportions were compared using the chi-squared test. An exploratory analysis of the effects of pre-specified clinically relevant covariates on response to tirzepatide treatment was performed using linear regression. Univariate comparisons of 40-week outcomes between multiple groups were performed using an analysis of variance with post-hoc testing by Tukey's HSD test. Statistical significance was assessed at $p < .05$. As the study design included all individuals initiating tirzepatide, no power calculation was performed. While all individuals included had complete data for weight and HbA1c at baseline and 40 weeks, missing data at the 12- and 28-week time points, accounting for 17% of the data, was multiply imputed using the *mice* package. While imputed data at the 12- and 28-week time points is reported for descriptive purposes, statistical analyses and assessments of the achievement of treatment goals were limited to the 40-week time point.

3 | RESULTS

From 24 October 2022 to 31 December 2023, 8945 patients were dispensed tirzepatide at ICLDC, of whom 86.0% were Emirati Arab, 9.5% were other Arab and 4.5% were other ethnicity; 8236 of these had complete baseline clinical data (Table S1). Of these, 3686 individuals had complete data for weight and HbA1c at 0 and 40 weeks, while 2028 individuals had complete data for weight and HbA1c at 0, 12, 28 and 40 weeks post-tirzepatide initiation, excluding individuals found not to have initiated treatment (Figure S1). Baseline characteristics for the 3686 individuals with initiation and 40-week data

TABLE 1 Baseline characteristics for all individuals dispensed tirzepatide with complete data at initiation and 40 weeks.

Characteristic	Total	Never GLP-RA	GLP-RA >1 year ago	Other GLP-RA	SC semaglutide
Count	3686	455	935	687	1609
Male	1504 (40.8)	214 (47.0)	368 (39.4)	275 (40.0)	647 (40.2)
Female	2182 (59.2)	241 (53.0)	567 (60.6)	412 (60.0)	962 (59.8)
Age, years	54.1 ± 11.5	53.1 ± 12.9	52.8 ± 11.8	57.4 ± 10.8	53.7 ± 10.9
Diabetes duration, years	10.6 ± 8.2	6.3 ± 7.2	10.7 ± 7.9	12.9 ± 8.5	10.7 ± 8.1
HbA1c, %	7.3 ± 1.5	7.3 ± 1.5	7.8 ± 1.7	7.5 ± 1.4	7.0 ± 1.3
BMI, kg/m^2	34.6 ± 6.0	33.7 ± 5.7	35.4 ± 6.4	34.5 ± 5.7	34.4 ± 6.0
Weight, kg	91.8 ± 17.7	90.2 ± 18.5	94.0 ± 18.5	90.5 ± 16.0	91.5 ± 17.5
Bariatric surgery	317 (8.6)	23 (5.1)	101 (10.8)	40 (5.8)	153 (9.5)
SBP, mmHg	124.9 ± 12.9	126.3 ± 13.9	126.7 ± 13.7	125.6 ± 11.7	123.1 ± 12.4
DBP, mmHg	74.0 ± 8.5	75.2 ± 8.8	74.8 ± 8.8	72.6 ± 8.7	73.8 ± 8.0
Pulse, min^{-1}	80.8 ± 14.6	79.8 ± 10.2	81.0 ± 11.5	79.8 ± 9.7	81.4 ± 18.4
Creatinine, μmol/L	70.8 ± 26.2	72.6 ± 24.8	70.3 ± 30.9	72.0 ± 23.0	70.0 ± 24.9
eGFR, ml/min/1.73 m^2	97.3 ± 19.2	97.1 ± 20.7	98.9 ± 19.3	93.7 ± 19.5	98.1 ± 18.3
eGFR, <60 ml/min/1.73 m^2	221 (6.1)	33 (7.5)	55 (6)	57 (8.3)	76 (4.8)
TC, mmol/L	4.1 ± 1.1	4.3 ± 1.1	4.4 ± 1.2	3.9 ± 1.0	3.9 ± 1.0
LDL, mmol/L	2.4 ± 0.9	2.6 ± 1.0	2.6 ± 1.0	2.2 ± 0.8	2.2 ± 0.8
ALT, IU/L	25.9 ± 16.8	29.8 ± 21.0	26.5 ± 18.3	24.8 ± 13.3	25.1 ± 15.8
ALP, IU/L	79.8 ± 23.8	80.8 ± 24.4	83.1 ± 23.1	79.4 ± 26.3	77.9 ± 22.7
Insulin	1113 (30.2)	80 (17.6)	306 (32.7)	253 (36.8)	474 (29.5)
Metformin	3083 (83.6)	365 (80.2)	762 (81.5)	617 (89.8)	1339 (83.2)
SGLT2i	2624 (71.2)	277 (60.9)	643 (68.8)	567 (82.5)	1137 (70.7)
Sulphonylurea	1056 (28.6)	108 (23.7)	245 (26.2)	265 (38.6)	438 (27.2)
Thiazolidinedione	796 (21.6)	74 (16.3)	200 (21.4)	190 (27.7)	332 (20.6)
DPP4i	661 (17.9)	172 (37.8)	204 (21.8)	108 (15.7)	177 (11.0)
Tirzepatide discontinued	724 (19.6)	114 (25.1)	207 (22.1)	132 (19.2)	271 (16.8)

Note: Stratified by previous GLP-RA status and combined. 'Never GLP-RA', no record of ever being dispensed any GLP-RA, 'GLP-RA >1 year ago', previous GLP-RA exposure but none in the preceding year before tirzepatide initiation, 'Other GLP-RA', directly switched from liraglutide, lixisenatide, dulaglutide or oral semaglutide.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-RA, glucagon-like peptide receptor agonist; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein; SBP, systolic blood pressure; SC, subcutaneous; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TC, total cholesterol.

are presented in Table 1. The majority of 3231 (87.8%) individuals were directly switched to tirzepatide from a GLP-RA, and 1609 (43.6%) from subcutaneous semaglutide. At initiation, metformin was used by 3083 (83.6%) patients, sulphonylurea by 1056 (28.6%), thiazolidinedione by 796 (21.6%), dipeptidyl peptidase-4 inhibitor (DPP4i) by 661 (17.9%), sodium-glucose cotransporter 2 inhibitor (SGLT2i) by 2624 (71.2%) and insulin by 1113 (30.2%). Of 317 (8.6%) individuals with a history of MBS, 226 (71.3%) reported sleeve gastrectomy, 72 (22.7%) gastric bypass and 19 (6.0%) other or unknown procedures.

3.1 | Tirzepatide dose titration

The mean tirzepatide dose dispensed was: 3.9 ± 1.9 mg/week during the initiation period; 7.2 ± 2.5 mg/week at 12 weeks; 7.6 ± 3.1 mg/week at 28 weeks; and 8.8 ± 3.7 mg/week at 40 weeks. Use of higher doses was limited by drug availability, and titration was more gradual than that performed during clinical trials. Of all individuals who initiated tirzepatide: at 40 weeks 122 (3.3%) were using 2.5 mg/week; 668 (18.1%) 5.0 mg/week; 530 (14.4%) 7.5 mg/week; 655 (17.8%) 10 mg/week; 370 (10.0%) 12.5 mg/week; and 529 (14.4%) 15 mg/week.

3.2 | Intention to treat

In the study population as a whole, the mean ± SD HbA1c was: 7.3 ± 1.5% at initiation; 6.7 ± 1.3 at 12 weeks; 6.7 ± 1.4% at 28 weeks; and 6.8 ± 1.5% at 40 weeks. The mean reduction in HbA1c was 0.6 ± 1.0% at 12 weeks, 0.6 ± 1.2% at 28 weeks and 0.6 ± 1.2% at 40 weeks. At 40 weeks, 2361 (64.1%) participants had HbA1c <7.0%,

TABLE 2 HbA1c outcomes at 40 weeks stratified by tirzepatide discontinuation, previous GLP-RA exposure and metabolic bariatric surgery status.

Group	Initial HbA1c, %	40 weeks HbA1c, %	Δ HbA1c, %	HbA1c <5.7%	HbA1c ≤6.5%	HbA1c <7.0%	Δ HbA1c ≥1.0%
Intention to treat (3686)	7.3 ± 1.5	6.8 ± 1.5	−0.6 ± 1.2	887 (24.1%)	1981 (53.7%)	2361 (64.1%)	1063 (28.8%)
Continued (2962)	7.3 ± 1.5	6.6 ± 1.4	−0.7 ± 1.2	785 (26.5%)	1684 (56.9%)	1994 (67.3%)	954 (32.2%)
Discontinued (724)	7.4 ± 1.5	7.3 ± 1.6	−0.1 ± 1.2	102 (14.1%)	297 (41%)	367 (50.7%)	109 (15.1%)
Never (455)	7.3 ± 1.5	6.4 ± 1.4	−1.0 ± 1.3	147 (32.3%)	313 (68.8%)	347 (76.3%)	183 (40.2%)
>1 year ago (935)	7.8 ± 1.7	7.0 ± 1.6	−0.8 ± 1.4	189 (20.2%)	464 (49.6%)	552 (59%)	360 (38.5%)
Other (687)	7.5 ± 1.4	6.9 ± 1.4	−0.6 ± 1.2	122 (17.8%)	311 (45.3%)	396 (57.6%)	201 (29.3%)
Semaglutide (1609)	7.0 ± 1.3	6.7 ± 1.4	−0.3 ± 1.1	429 (26.7%)	893 (55.5%)	1066 (66.3%)	319 (19.8%)
No surgery (3369)	7.4 ± 1.5	6.8 ± 1.5	−0.6 ± 1.3	730 (21.7%)	1722 (51.1%)	2085 (61.9%)	988 (29.3%)
Bariatric surg. (317)	6.5 ± 1.3	5.9 ± 1.1	−0.6 ± 1.0	157 (49.5%)	259 (81.7%)	276 (87.1%)	75 (23.7%)

Note: 'Never', no record of ever being dispensed any GLP-RA; '>1 year ago', previous GLP-RA exposure but none in the preceding year before tirzepatide initiation; 'other', directly switched to tirzepatide from liraglutide, lixisenatide, dulaglutide or oral semaglutide; 'semaglutide', subcutaneous semaglutide.
Abbreviations: GLP-RA, glucagon-like peptide receptor agonist; HbA1c, glycated haemoglobin.

TABLE 3 Weight outcomes at 40 weeks stratified by previous glucagon-like peptide receptor agonist exposure and metabolic bariatric surgery status.

Group	Initial weight, kg	40-week weight, kg	Δ Weight 40 weeks, kg	Δ Weight 40 weeks, %	Weight reduction ≥5.0%	Weight reduction ≥10.0%	Weight reduction ≥15.0%	Weight reduction ≥20.0%
Intention to treat (3686)	91.8 ± 17.7	87.3 ± 17.5	−4.5 ± 6.9	−4.8 ± 7.3	1590 (43.1%)	749 (20.3%)	318 (8.6%)	115 (3.1%)
Continued (2962)	92.6 ± 17.8	87.4 ± 17.7	−5.3 ± 6.9	−5.6 ± 7.2	1427 (48.2%)	689 (23.3%)	294 (9.9%)	105 (3.5%)
Discontinued (724)	88.3 ± 17.8	86.8 ± 17.0	−1.5 ± 6.2	−1.5 ± 6.7	163 (22.5%)	60 (8.3%)	24 (3.3%)	10 (1.4%)
Never (455)	90.2 ± 18.5	83.0 ± 16.4	−7.2 ± 8.6	−7.5 ± 8.1	272 (59.8%)	166 (36.5%)	76 (16.7%)	27 (5.9%)
>1 year (935)	94.0 ± 18.5	89.3 ± 18.7	−4.6 ± 6.9	−4.8 ± 7.1	413 (44.2%)	193 (20.6%)	76 (8.1%)	26 (2.8%)
Other (687)	90.5 ± 16.0	86.0 ± 16.0	−4.5 ± 5.5	−5.0 ± 6.1	315 (45.9%)	125 (18.2%)	44 (6.4%)	10 (1.5%)
Semaglutide (1609)	91.5 ± 17.5	87.8 ± 17.6	−3.7 ± 6.8	−3.9 ± 7.4	590 (36.7%)	265 (16.5%)	122 (7.6%)	52 (3.2%)
No surgery (3369)	91.7 ± 17.5	87.4 ± 17.4	−4.2 ± 6.6	−4.5 ± 7.0	1412 (41.9%)	624 (18.5%)	246 (7.3%)	84 (2.5%)
Bariatric surg. (317)	93.0 ± 18.9	85.2 ± 18.8	−7.8 ± 9.4	−8.1 ± 9.3	178 (56.2%)	125 (39.4%)	72 (22.7%)	31 (9.8%)

Note: 'Never', no record of ever being dispensed any glucagon-like peptide receptor agonist; '>1 year ago', previous glucagon-like peptide receptor agonist exposure but none in the preceding year before tirzepatide initiation; 'other', directly switched to tirzepatide from liraglutide, lixisenatide, dulaglutide or oral semaglutide; 'semaglutide', subcutaneous semaglutide.

1981 (53.7%) had HbA1c ≤6.5% and 887 (24.1%) had HbA1c <5.7%, compared with 1734 (47.0%), 1271 (34.5%) and 378 (10.3%) at initiation, respectively. A 1.0% reduction in HbA1c from baseline was achieved in 626 (24.8%) at 12 weeks, 762 (28.2%) at 28 weeks and 1063 (28.8%) at 40 weeks (Table 2).

The mean weight was 91.8 ± 17.7 kg at initiation, 89.0 ± 17.5 kg at 12 weeks, 87.7 ± 17.6 kg at 28 weeks and 87.3 ± 1754 kg at 40 weeks. The mean weight reduction was 2.7 ± 4.2 kg at 12 weeks, 4.2 ± 5.8 kg at 28 weeks and 4.5 ± 6.9 kg at 40 weeks, while the mean percentage weight reduction was 2.9 ± 4.5% at 12 weeks, 4.5 ± 6.1% at 28 weeks and 4.8 ± 7.3% at 40 weeks. At 40 weeks, a ≥5% weight reduction was achieved in 1590 (43.1%), ≥10% in 749 (20.3%), ≥15% in 318 (8.6%) and ≥20% in 115 (3.1%) individuals (Table 3).

Statistically and clinically significant improvements were observed in blood pressure, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides at 40 weeks. Systolic blood pressure decreased by 3.7 ± 13.0 mmHg ($p < .0001$, paired t-test). Total cholesterol reduced by 0.3 ± 1.0 mmol/L, LDL-C by 0.2 ± 0.9 mmol/L and triglycerides by 0.2 ± 0.9 mmol/L ($p < .0001$ for all, paired t-test). There was a statistically significant but clinically insignificant increase

TABLE 4 Reasons for discontinuation of tirzepatide treatment in 724 individuals.

Reason for discontinuation	n	Side effect description	n
Individuals with ≥1 adverse event	288		
GI upset	228	Nausea	180
		Vomiting	28
		Diarrhoea	24
		Abdominal pain	18
		Abdominal bloating	10
		Constipation	5
		Reflux	4
		Loss of appetite	3
Patient decision	188	Prefers other GLP-RA	101
		Other patient preference	14
		Prefers oral therapy	18
		Failure to lose weight	12
		Excessive weight loss	13
		No effect on appetite	2
		Concern about potential thyroid cancer risk	2
		No improvement in glucose	3
Not recorded/unclear	125		
Non-GI side effect	65	Fatigue	12
		Mood change	9
		Hypoglycaemia	7
		Dizziness	7
		Myalgia	6
		Skin rash/pruritus	6
		Injection site reaction	5
		Headache	3
		Excessive weight loss	3
		Numbness	2
Drug unavailable	50		
Medical decision	20	No improvement in blood glucose	9
		Excellent glycaemic control	2
		Thyroid nodule	2
		Decline in eGFR	2
		Change in diabetes diagnosis	1
		Uncontrolled hyperglycaemia	1
		Elevated liver transaminases	1
Funding withdrawn	19		
Planned pregnancy	11		
Pregnancy	8		
Hospital attendance or admission	6		
Bariatric surgery	6		
Pancreatitis	1		

Abbreviations: eGFR, estimated glomerular filtration rate; GI, gastrointestinal.

in eGFR at 40 weeks of 0.8 ± 7.0 ml/min/1.73 m^2 ($p < .0001$, paired t-test). Because of a limitation of the electronic medical record, dosage for individual lipid-lowering medications was not accessible, but records of newly initiated agents were retrieved: 111 individuals initiated statins, 258 initiated ezetimibe, five initiated alirocumab and 39 initiated inclisiran. Adjusted for these medications and for previous

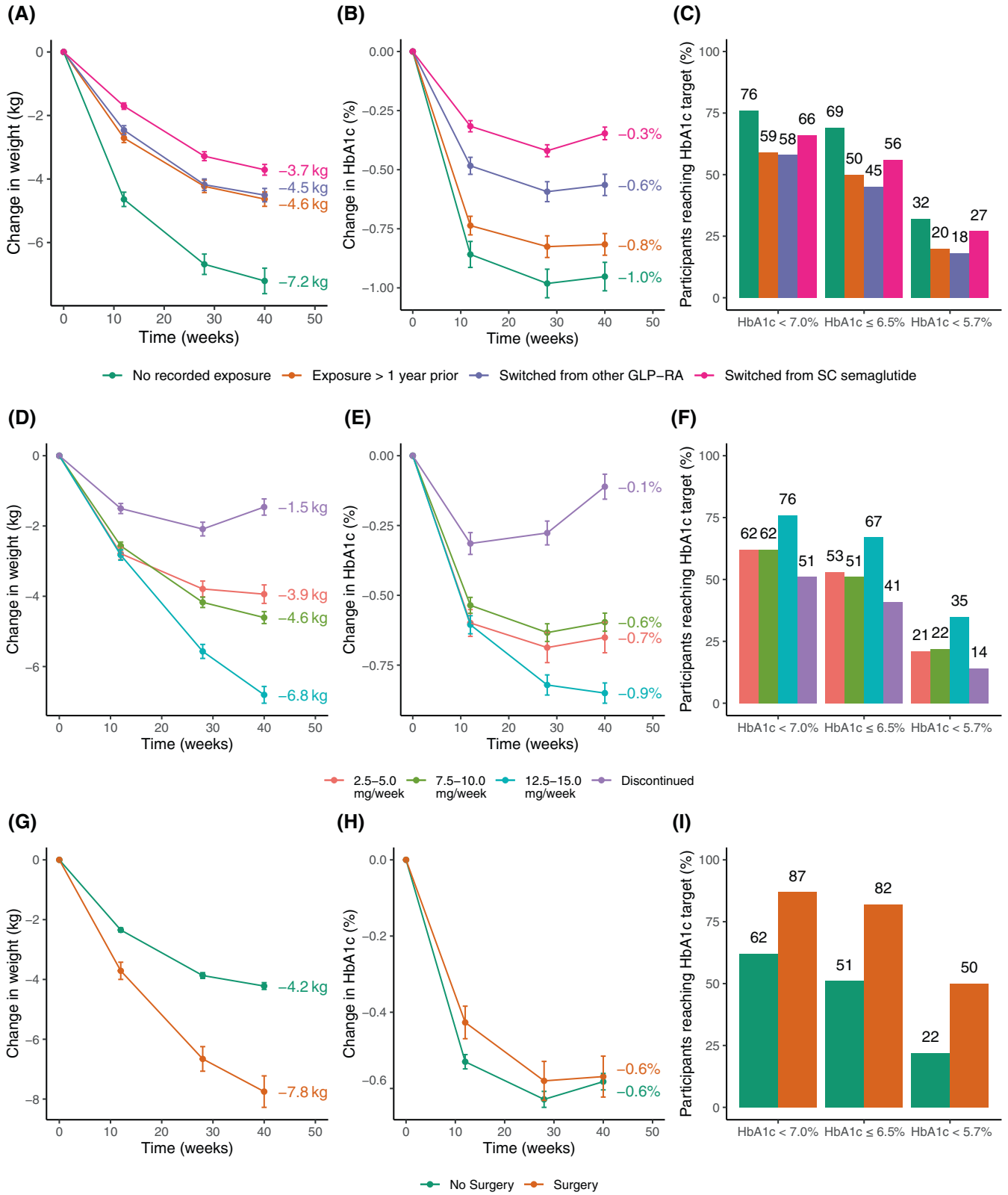

FIGURE 1 HbA1c and weight endpoints stratified by study groups. (A-C) Change in weight, change in HbA1c and achievement of HbA1c targets by previous glucagon-like peptide receptor agonist treatment. (D-F) Change in weight, change in HbA1c and achievement of HbA1c targets by highest tirzepatide dose dispensed. (G-I) Change in weight, change in HbA1c and achievement of HbA1c targets by metabolic bariatric surgery status. Mean ± SEM or proportion are displayed. 17% of interim (12- and 28-week) data were imputed. HbA1c, glycated haemoglobin.

GLP-RA exposure, individuals who achieved tirzepatide doses of 7.5-10.0 mg/week or ≥12.5 mg/week had significantly greater LDL-C reduction than those who discontinued treatment at 40 weeks [−0.14 (−0.22 to −0.07), $p < .001$; −0.16 (−0.24 to −0.08), $p < .001$]. Initiation of a statin or inclisiran was associated with greater LDL-C reduction [−0.31 (−0.48 to −0.14), $p < .001$; −0.67 (−0.95 to −0.4), $p < .001$], while LDL reduction in individuals directly switched from subcutaneous semaglutide or other GLP-RA was less than in those with no previous GLP-RA exposure [0.21 (0.11 to 0.30), $p < .001$; 0.15 (0.05 to 0.26), $p < .01$].

There was a slight and significant reduction in alanine aminotransferase (ALT) of 2.6 ± 16.3 IU/L ($p < .0001$, paired t-test), while in 854 individuals with ALT >30 IU/L at initiation, the reduction in ALT at 40 weeks was 10.9 ± 26.3 IU/L ($p < .0001$, paired t-test). Of a subset of male participants with ALT >30 IU/L and female patients with ALT >19 IU/L at initiation (n = 1140), 421 (37%) achieved ALT below their sex-specific ALT target at week 40.

We observed a reduction in the number of concomitant hypoglycaemic medications after the initiation of tirzepatide. At 40 weeks, metformin was confirmed discontinued in 183 individuals (5.9% of those using metformin at tirzepatide initiation), sulphonylurea in 253 (23.6%), DPP4i in 510 (69.7%), SGLT2i in 149 (5.6%), thiazolidinedione in 105 (12.9%) and insulin in 109 (9.6%).

3.3 | Effects of the maximum attained tirzepatide dosage and discontinuation

One thousand and fifty-two individuals were titrated to a maximum tirzepatide dose of 12.5 or 15.0 mg/week ('high' dose), 1402 to a maximum dose of 7.5 or 10.0 mg/week ('intermediate' dose), and 508 to a maximum of 2.5 or 5.0 mg/week ('low') dose. Tirzepatide was confirmed to have been discontinued in 724 individuals (19.6%) during the 40-week follow-up period (Table 4). At 40 weeks, HbA1c was 7.3 ± 1.6% in individuals who discontinued treatment, 6.9 ± 1.6 in the low-dose group, 6.8 ± 1.5% in the intermediate-dose group and 6.3 ± 1.2% in the high-dose group. In the high-dose group, 802 (76.2%) achieved HbA1c <7.0% and 702 (66.7%) achieved HbA1c ≤6.5% compared with 875 (62.4%) achieving <7.0% and 713 (50.9%) achieving ≤6.5% in the intermediate-dose group, 317 (62.4%) achieving <7.0% and 269 (53.0%) achieving ≤6.5% in the low-dose group and 367 (50.2%) achieving <7.0% and 297 (41.0%) achieving ≤6.5% in the discontinuation group (Table 2, Figure 1E,F). The change in HbA1c at 40 weeks differed significantly between all pairs of dosage groups ($p < .05$) with the exception of the low-dose and intermediate-dose groups ($p = .81$).

The mean weight reduction at 40 weeks was 6.8 ± 7.7 kg in the high-dose group, 4.6 ± 6.4 kg in the intermediate-dose group, and 3.9 ± 5.9 kg in the low-dose group, compared with 1.5 ± 6.2 kg in the discontinuation group. Percentage weight reduction at 40 weeks was 7.0 ± 7.9% in the high-dose group, 4.9 ± 6.6% in the intermediate-dose group, 4.6 ± 6.7% in the low-dose group and 1.5 ± 6.7% in the discontinuation group. At 40 weeks, 30.8% of individuals in the high-dose group achieved ≥10.0% weight reduction, compared with 19.2% in the intermediate-dose group, 18.9% in the low-dose group and 8.4% in the discontinuation group (Table 3, Figure 1D). The change in weight at 40 weeks differed significantly between all pairs of groups ($p < .0001$) with the exception of the low-dose and intermediate-dose groups ($p = .21$).

3.4 | Effect of previous glucagon-like peptide-1 receptor agonist treatment

The mean reduction in HbA1c at 40 weeks was 0.3 ± 1.1% in individuals switched to tirzepatide from subcutaneous semaglutide, 0.6 ± 1.2% in individuals switched from another subcutaneous GLP-RA or oral semaglutide ('other GLP-RA'), 0.8 ± 1.4% in individuals not directly switched but with history of GLP-RA exposure >1 year previously to the date of commencing tirzepatide ('previous exposure'), and 1.0 ± 1.3% in individuals with no record of any previous exposure to GLP-RA ('naïve') (Figure 1B). The mean HbA1c reduction at 40 weeks was significantly greater in the naïve group than in the subcutaneous semaglutide group ($p < .0001$) or the other GLP-RA group ($p < .0001$) but not in the previous exposure group ($p = .073$). At 40 weeks, 76.3% of individuals with no previous exposure to GLP-RA had HbA1c <7.0% and 68.8% had HbA1c ≤6.5%, compared with 59.0% (<7.0%) and 49.6% (≤6.5%) of those with previous GLP-RA exposure, 57.6% (<7.0%) and 45.3% (≤6.5%) of those directly switched from another GLP-RA, and 66.3% (<7.0%) and 55.5% (≤6.5%) of those switched from subcutaneous semaglutide (Table 2, Figure 1B,C).

The mean reduction in weight at 40 weeks was 3.7 ± 6.8 kg in the subcutaneous semaglutide group, 4.5 ± 5.5 kg in the other GLP-RA group, 4.6 ± 6.9 kg in the previous exposure group, and 7.2 ± 8.6 kg in the GLP-RA-naïve group (Figure 1A). Although baseline weight was lowest in the naïve group (90.2 ± 18.5 kg naïve, 94.0 ± 18.5 kg previous exposure, 90.5 ± 16.0 kg other GLP-RA, 91.5 ± 17.6 kg subcutaneous semaglutide), change in weight at 40 weeks was significantly greater in GLP-RA-naïve individuals than in any other group ($p < .0001$, all comparisons). At 40 weeks, 36.5% of individuals in the naïve group achieved >10% weight reduction, compared with 20.6% in the previous exposure group, 18.2% in the other GLP-RA group, and 16.6% in the subcutaneous semaglutide group (Table 3, Figure 1A).

3.5 | Individuals with a previous history of metabolic bariatric surgery

The mean HbA1c at initiation was 6.5 ± 1.3% in 317 individuals with a previous history of MBS, compared with 7.4 ± 1.5% in 3369 individuals without (NoS) ($p < .0001$). At 40 weeks, the mean reduction in HbA1c was 0.6 ± 1.0% in the MBS group and 0.6 ± 1.3% in the NoS group ($p = .81$) (Figure 1H). At 40 weeks, 87.1% of individuals in the MBS group had HbA1c <7.0%, compared with 61.9% in the NoS

group, although, importantly, a larger proportion in the baseline group were already at this target at baseline (75.7%; NoS: 44.3%) (Table 2, Figure 1H,I).

The mean weight at baseline was 93.0 ± 18.8 kg in the MBS group and 91.7 ± 17.5 kg in the NoS group ($p = .24$, not significant). The mean reduction in weight at 40 weeks was 7.8 ± 9.4 kg in the MBS group compared with 4.2 ± 6.6 kg in the NoS group ($p < .0001$) (Figure 1G), while the mean percentage reduction in weight was 8.1 ± 9.3% in the MBS group and 4.5 ± 7.0% in the NoS group. A larger proportion of individuals in the MBS group achieved a 10% weight reduction at 40 weeks than in the NoS group (MBS: 39.4%; NoS: 18.5%; $p < .0001$) (Table 3, Figure 1G).

3.6 | Safety and tolerability

In total, 724 (19.6%) individuals discontinued treatment. Adverse events were the cause of discontinuation in 288 individuals (39.7% of discontinuations; 7.8% of those treated). The reason for discontinuation was not clear from the medical record in 125 cases, and other reasons were given in 311 cases. Reasons for discontinuation are presented in Table 4. Hypoglycaemia was the reason for discontinuation in seven (0.2%) patients. Gastrointestinal (GI) side effects were the most common reason for discontinuation, being reported in 228 (31.5%). The most common GI side effects were nausea (180), vomiting (28) and diarrhoea (24) while the commonest non-GI side effects were fatigue (12), mood change (nine), pruritus or skin rash (six), myalgia (six) and injection site reactions (five). Six patients reported attendance or admission at the hospital related to tirzepatide use.

The decision to discontinue was patient-led in 188 cases (25.9%). The most common reason stated was a preference for an alternative GLP-RA, in 101 cases. Other reasons included failure to lose weight (12), excessive weight loss (13), the decision with proceed to MBS (six), no effect on appetite (two) and concern about the theoretical relationship between GLP-RAs and thyroid cancer (two). In 20 cases, the patient's physician decided to stop treatment, with the stated reasons being no improvement in blood glucose in nine cases, excellent glycaemic control in two cases, newly-diagnosed thyroid nodules in two cases, interim decline in eGFR in two cases, elevation of liver transaminases in one case, lack of effect on glucose in one case and a change in diabetes diagnosis from type 2 to type 1 diabetes based on low stimulated C-peptide in one case. Funding was withdrawn in 19 cases, and in 50 cases, the drug was discontinued because of its unavailability.

One participant who was switched from subcutaneous semaglutide to tirzepatide 2 months previously was admitted to the hospital with abdominal pain, and a diagnosis of acute pancreatitis was confirmed based on raised serum lipase and computed tomography findings. A simultaneous diagnosis of euglycaemic diabetic ketoacidosis was also made. This patient had a preceding history of gallstone pancreatitis, although no gallstones were seen on subsequent magnetic resonance cholangiopancreatography.

The majority of individuals discontinuing treatment did not receive a dose of tirzepatide >5.0 mg/week (n = 403, 56%), while only 35 of 1087 (3.2%) individuals whose maximum dispensed dose of tirzepatide was 12.5 or 15.0 mg/week discontinued treatment. Tirzepatide was discontinued in 271 of 1609 (16.8%) individuals who were switched from subcutaneous semaglutide, 132 of 687 (19.2%) of those switched from another GLP-RA, 207 of 935 (22.1%) of individuals with other previous history of GLP-RA exposure and 114 of 455 (25.1%) of GLP-RA-naïve individuals. The difference in proportion of discontinuations between individuals switching directly from another GLP-RA (17.6%) compared with those without recent or ever GLP-RA exposure (23.1%) was significant ($p < .0001$).

3.7 | Exploratory endpoints: predictors of response to tirzepatide

The effects of baseline characteristics, maximum dispensed tirzepatide dose and tirzepatide discontinuation on HbA1c and weight at 40 weeks of initiation were explored using multiple linear regression, adjusted for initial HbA1c or weight, previous GLP-RA exposure, MBS status, use of insulin, sulphonylurea or thiazolidinedione at the time of tirzepatide initiation, discontinuation of tirzepatide, and diabetes duration (less or greater than 10 years).

3.7.1 | Glycated haemoglobin outcomes

Previous exposure to a GLP-RA was significantly associated with higher HbA1c at 40 weeks when compared with individuals with no record of GLP-RA exposure [ever exposed 0.32 (0.21 to 0.44)%, $p < .0001$; other 0.43 (0.31 to 0.56)%, $p < .0001$; and subcutaneous semaglutide 0.56 (0.44 to 0.67)%, $p < .0001$]. Use of insulin, sulphonylurea or a DPP4i at initiation, diabetes duration >10 years, and discontinuation of tirzepatide were associated with a significantly higher 40-week HbA1c, while HbA1c was significantly lower in individuals with previous history of MBS [−0.24 (−0.37 to −0.12)%, $p < .0001$], and significantly lower in individuals who attained a maximum tirzepatide dose ≥12.5 mg/week compared with those treated with ≤5.0 mg/week [−0.41 (−0.51 to −0.31)%, $p < .0001$]. The fully-adjusted model explained 30% of the variability in the outcome ($r^2 = 0.295$) (Figure S2a).

3.7.2 | Weight outcomes

Previous GLP-RA exposure was associated with significantly higher weight at 40 weeks than in individuals with no exposure [ever exposed 3.01 (2.28 to 3.74) kg, $p < .0001$, other GLP-RA 2.83 (2.05 to 3.62) kg, $p < .0001$, subcutaneous semaglutide 4.24 (3.55 to 4.94) kg, $p < .0001$]. Previous MBS, maximum tirzepatide dose 7.5-10.0 mg/week, and maximum tirzepatide dose ≥12.5 mg/week were significantly associated with lower weight at 40 weeks [baseline: −3.11

(−3.86 to −2.36) kg, $p < .0001$; maximum tirzepatide dose 7.5–10.0 mg/week −0.69 (−1.24 to −0.15), $p < .05$; maximum dose ≥12.5 mg/week −2.82 (−3.45 to −2.19), $p < .0001$]. Insulin or sulphonylurea use at initiation, diabetes duration >10 years at initiation, and discontinuation of tirzepatide, were positively associated with weight at 40 weeks. The fully-adjusted model explained 16% of the variability in the outcome ($r^2 = 0.165$) (Figure S2b).

4 | DISCUSSION

In this observational, real-world study, tirzepatide treatment resulted in reductions in HbA1c and weight as well as improvements in some cardiovascular risk factors. Following the publication of results from the phase 3 SURPASS studies,[1–5] the use of tirzepatide has been prioritized by international guidelines as the most effective treatment for both HbA1c and weight reduction.[6]

The United States Food and Drug Administration recognizes real-world studies as important in supporting regulatory decision-making.[7] Inclusion criteria for clinical trials may select participants with shorter disease duration, fewer medications used at baseline and fewer comorbidities, and trial protocols may provide superior access to resources and support to comply with treatment. Consequently, the efficacy of interventions reported in clinical trials often exceeds their real-world effectiveness.[8]

Although statistically and clinically significant, the reductions in HbA1c and weight we observed were numerically less than those reported in the SURPASS-2 study.[2] However, participants in SURPASS-2 were treatment-naïve to GLP-RAs, used metformin monotherapy, reached higher doses of tirzepatide and received a longer course of treatment. Our real-world cohort, of predominantly Emirati Arab origin, predominantly switched from GLP-RAs, used multiple concomitant antihyperglycaemic medications, and reached a mean maximum tirzepatide dose of 9.7 ± 3.6 mg/week. Although baseline BMI in our cohort was comparable with the SURPASS studies, baseline glycaemic control was considerably better in our patients, which may have limited the potential for further HbA1c reduction with tirzeptide.

Patients who were naïve to GLP-RA therapy experienced greater HbA1c and weight reductions than those switching from other GLP-RAs. Switching between GLP-RAs is common in clinical practice for reasons including effectiveness, side effect profile, or drug availability.[9] Because of a global shortage that coincided with the availability of tirzepatide, the majority of new users of tirzepatide in our study were ex-users of subcutaneous semaglutide. Among other studies, the SUSTAIN trial programme, EXPERT and REALIZE DM showed improvements in HbA1c when switching from other GLP-RAs to subcutaneous semaglutide.[2,10–14] Consistent with this, we observed greater HbA1c and weight responses in those switching from less effective GLP-RAs than in those switching from subcutaneous semaglutide. Interestingly, we also found that individuals with previous, but not recent, GLP-RA exposure experienced significantly lesser reductions in HbA1c and weight than GLP-RA-naïve individuals, adjusted for other clinical variables and concomitant medications. While this could potentially be because of confounding by other clinical factors, the possibility of an effect of tachyphylaxis at the GLP-1 receptor remains.[15] Our data provide real-world evidence that switching to tirzepatide from other GLP-RAs resulted in further improvements in HbA1c and weight.

Nine per cent of our cohort had MBS before tirzepatide initiation. Despite a comparable baseline BMI with the non-surgical group, the BMI reduction after 6 months of treatment with tirzepatide was significantly greater in the MBS group. Weight regain or inadequate weight loss after MBS is common, and our results suggest that tirzepatide can be an effective option for post-MBS patients.[16,17]

We observed significant improvements in blood pressure and lipid profile after the initiation of tirzepatide. Diabetes treatments that improve not only glycaemia but also weight, blood pressure and lipids may reduce the risk of cardiovascular complications from diabetes.[18] In a pre-specified meta-analysis of the seven randomized controlled trials in the SURPASS programme (with a duration of ≥26 weeks, including 4887 patients treated with tirzepatide and 2328 treated with comparators), major adverse cardiovascular events were reduced by 20% (HR 0.80).[19] A prospective cardiovascular outcome trial, SURPASS-CVOT,[20] is expected to be completed in 2024. The reduction in ALT we observed was consistent with previous studies.[3,21] Given that our cohort had mean baseline ALT within the reference range, it will be interesting to see the effect of tirzepatide therapy in patients with high ALT levels in the ongoing SYNERGY-NASH study.[22]

In this real-world study, tirzepatide was well tolerated in the majority of cases, and the rate of discontinuation because of side effects was comparable with that reported in the SURPASS programme and other GLP-RA studies.[23–25] The combined discontinuation rate of 19.6% was comparable with that reported in other real-world studies of GLP-RA treatment.[26] Although 30% of participants were treated with insulin and 29% with SUs, only seven patients reported hypoglycaemia as a reason for discontinuation of tirzepatide, consistent with results from the SURPASS-4 and SURPASS-5 studies.[4,5] Further real-world data on safety, patient acceptability and adherence would be important and of clinical interest.

A major strength of our study is the availability of many important, real-world, clinical outcomes from a large number of patients with type 2 diabetes initiating tirzepatide. To our knowledge, this study is the first to provide real-world evidence of the effectiveness of tirzepatide for those switching from other GLP-RAs. Although this was a review of real-world clinical data, the study was designed and study endpoints were specified before the introduction of tirzepatide at our centre.

The limitations of this study included the observational design, the restriction to a single centre and the inability to assess concordance with treatment. The mean HbA1c at the initiation of tirzepatide was lower than in the SURPASS studies, and a relatively large proportion of participants already met glycaemic targets at tirzepatide initiation. Fewer patients reached the top tirzepatide doses of 12.5 and 15 mg, and the duration of treatment at these doses and dose

titration were slower than in the SURPASS studies. The study follow-up period was too short to assess the effects of tirzepatide on microvascular and macrovascular endpoints. As tolerability assessment was limited to individuals who discontinued treatment, mild-to-moderate side effects of tirzepatide would probably have been under-reported.

5 | CONCLUSIONS

In conclusion, this real-world study found that tirzepatide use in predominantly Emirati Arab patients with type 2 diabetes who are naïve to GLP-1 RA resulted in clinically meaningful reductions in HbA1c levels and weight, as well as improvements in blood pressure and lipid profile, and was well tolerated, in line with previously published data from randomized controlled trials. In patients who were switched from other GLP-1 RA to tirzepatide, additional glycaemic and weight loss benefits were observed. Finally, patients who previously had MBS appeared to benefit more in terms of weight reduction. Future research should examine the use of tirzepatide in the real world for longer periods and in larger numbers to ascertain its effects on hard clinical endpoints such as cardiovascular disease and microvascular complications, and findings should be interpreted in the context of previous GLP-RA exposure and MBS status.

AUTHOR CONTRIBUTIONS

MS designed the study and wrote the first draft of the manuscript. AB performed statistical analysis and contributed to the first draft of the manuscript. MS, AB, MA and NM performed data collection from the medical record. NL, NM, MA and SS contributed to the study design and reviewed, edited and approved the final version of the manuscript. CIR reviewed, edited and approved the final version of the manuscript. AB had access to all of the data used in this project and is the guarantor. The manuscript was approved for submission by all authors.

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CONFLICT OF INTEREST STATEMENT

CIR reports grants from the Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research Board. He serves on advisory boards and speakers' panels of Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Glia, Irish Life Health, Boehringer Ingelheim, Currax, Zealand Pharma and Rhythm Pharma. CIR is a member of the Irish Society for Nutrition and Metabolism outside the area of work commented on here. He was the chief medical officer and director of the Medical Device Division of Keyron in 2021. Both of these are unremunerated positions. CIR was a previous investor in Keyron, which develops endoscopically implantable medical devices intended to mimic the surgical procedures of sleeve gastrectomy and gastric bypass. No patients have been included in any of Keyron's studies and they are not listed on the stock market. CIR was gifted stock holdings in September 2021 and divested all stock holdings in Keyron in September 2021. He continues to provide scientific advice to Keyron for no remuneration. CIR provides obesity clinical care in the Beyond BMI clinic and is a shareholder in the clinic. The other authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15680.

DATA AVAILABILITY STATEMENT

Anonymised source data will be shared for projects where there is a reasonable expectation that it can be used to answer the research question. Detailed applications with full protocol and a clearly defined research question should be sent to abuckley@icldc.ae. Data provision will be subject to institutional agreements, contracts and national regulatory approval.

ORCID

Adam Buckley https://orcid.org/0000-0001-7471-0273
Carel W. le Roux https://orcid.org/0000-0001-5521-5445

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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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