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Review Article

Long-Term Follow-Up of GLP-1 receptor agonist therapy for type 2 diabetes mellitus

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Abstract

Background: GLP-1 receptor agonists (GLP-1RAs) are now foundational therapy for type 2 diabetes mellitus (T2DM), but long-term real-world durability data beyond three years remain limited. We report a five-year, multi-centre follow-up of GLP-1RA therapy in routine practice.

Methods: This retrospective cohort study followed 612 adults with T2DM initiating liraglutide, dulaglutide, semaglutide or exenatide across three centres, with structured assessment of HbA1c, weight, cardiometabolic risk and persistence to 60 months.

Results: Mean HbA1c fell 1.3 percentage points by 24 months (nadir 7.3%, $p < 0.001$), remaining 1.0 point below baseline at 60 months. Weight fell up to 4.6% before partial attenuation. Major cardiovascular events occurred at 18.7/1000 patient-years. Five-year persistence was 51%; gastrointestinal events drove early discontinuation.

Conclusion: GLP-1RA benefits on glycaemia, weight and cardiometabolic risk were largely sustained over five years of routine practice, with a safety profile consistent with randomised trials.

Keywords: GLP-1 receptor agonist; type 2 diabetes mellitus; long-term follow-up; glycaemic control; cardiovascular outcomes

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disease in which sustained glycaemic control, weight management and cardiovascular risk reduction must all be pursued simultaneously if long-term complications are to be avoided. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) act on pancreatic, gastric, hypothalamic and cardiovascular GLP-1 receptors to augment glucose-dependent insulin secretion, suppress glucagon release, slow gastric emptying and promote satiety, giving the class a mechanistic profile that addresses glycaemia and adiposity together rather than in isolation [1,2]. Since the introduction of exenatide and subsequently liraglutide, dulaglutide, semaglutide and lixisenatide, the class has moved from a second-line glucose-lowering option to a foundational therapy recommended early in the treatment algorithm for most adults with T2DM, particularly those with established atherosclerotic cardiovascular disease, chronic kidney disease or a high body-mass index [3,4,5,6].

That shift was driven substantially by large, randomised cardiovascular outcome trials. Liraglutide reduced the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke in the LEADER trial [7], semaglutide showed a similar benefit in SUSTAIN-6 [8], and once-weekly dulaglutide extended this signal to a broadly primary-prevention population in REWIND [9]. EXSCEL and PIONEER 6 were non-inferior to placebo without reaching superiority [10,11], while ELIXA and Harmony Outcomes rounded out a body of evidence supporting a favourable or neutral cardiovascular effect across the class [12,13]. A pooled meta-analysis of these trials confirmed reductions in major adverse cardiovascular events, cardiovascular and all-cause mortality, and a composite kidney outcome [14].

Most pivotal cardiovascular outcome trials followed patients for two to five years under closely monitored protocol conditions, and far less is published about how

glycaemic, weight and safety outcomes evolve when GLP-1RA therapy is followed in ordinary specialist practice over a comparable or longer horizon. We therefore undertook a long-term, multi-centre, retrospective follow-up of adults with T2DM initiating a GLP-1RA in routine endocrinology practice, characterising glycaemic control, body weight, cardiometabolic risk, major adverse cardiovascular and renal events, and treatment persistence over five years.

2. Methods

We conducted a retrospective longitudinal cohort study across three collaborating metabolic disease centres: the Tiber Institute of Diabetes and Endocrinology (Wales), the Clyde Research Center for Metabolic Disease (Canada) and the Narmada Academy of Metabolic Disease (Canada). Eligible patients were adults aged 18 years or older with a confirmed diagnosis of T2DM who initiated a GLP-1RA (liraglutide, exenatide, dulaglutide or semaglutide) as part of routine clinical care between January 2016 and December 2019, with at least one recorded follow-up visit beyond 12 months. Patients who had previously used a GLP-1RA, who were enrolled in an interventional drug trial during the follow-up window, or whose baseline glycated haemoglobin (HbA1c) or weight was not recorded within 90 days of initiation were excluded. Six hundred and twelve patients met these criteria and formed the analytic cohort.

Structured data were abstracted at baseline and at 6, 12, 24, 36, 48 and 60 months. Extracted variables included HbA1c, weight and body-mass index, blood pressure, lipids, estimated glomerular filtration rate (eGFR), concomitant medications, agent and dose, and adjudicated adverse events. Primary outcomes were change in HbA1c and weight from baseline. Secondary outcomes were the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke (MACE), a composite renal outcome (sustained eGFR decline of 40% or more, end-stage kidney disease, or renal

death), treatment persistence, and pre-specified adverse events including gastrointestinal events, pancreatitis, cholelithiasis and injection-site reactions.

Continuous outcomes were analysed using linear mixed-effects models with random intercepts per patient and centre, fixed effects for timepoint, baseline agent and baseline covariates, reported as adjusted mean change with 95% confidence intervals. Time-to-event outcomes were analysed by Kaplan-Meier estimation with incidence per 1000 patient-years, on an intention-to-treat basis retaining patients regardless of subsequent within-class agent switching. A two-sided p-value below 0.05 was considered significant. The study was approved by the institutional review boards of the three participating centres, with consent waived for this retrospective analysis of de-identified records.

3. Results

Cohort characteristics

Of the 612 patients included, the mean age at GLP-1RA initiation was 58.4 ± 10.2 years, 53% were female, and mean body-mass index was 34.1 ± 5.6 kg/m2. Mean duration of diagnosed T2DM was 9.7 years and mean baseline HbA1c was 8.6 ± 1.2%. Established atherosclerotic cardiovascular disease was present in 31% of the cohort and chronic kidney disease (eGFR below 60 mL/min/1.73m2) in 18%. Liraglutide was the index agent in 38% of patients, dulaglutide in 27%, semaglutide in 24% and exenatide in 11%, reflecting sequential availability of these agents across the recruitment window. Baseline cohort characteristics are summarised in Table 1.

Glycemic outcomes

Mean HbA1c fell from 8.6% at baseline to 7.6% at 6 months and reached a nadir of 7.3% at 24 months, an adjusted mean reduction of 1.3 percentage points (95% CI 1.1-1.5, p<0.001). The reduction attenuated modestly thereafter but remained clinically meaningful and statistically significant throughout follow-up, with a mean

reduction of 1.0 percentage point still present at 60 months relative to baseline (Figure 1). The proportion of patients achieving an HbA1c below 7.0% rose from 12% at baseline to a peak of 46% at 24 months before settling at approximately 38% at 60 months, a pattern consistent with partial treatment attenuation related to disease progression, intercurrent illness and, in a minority of patients, agent discontinuation rather than loss of drug efficacy in patients who remained on therapy.

Table 1: Baseline characteristics of the 612-patient long-term follow-up cohort by index GLP-1 receptor agonist.	
Characteristic	Value
Age, years (mean +/- SD)	58.4 +/- 10.2
Female sex	53%
Body-mass index, kg/m2 (mean +/- SD)	34.1 +/- 5.6
Duration of type 2 diabetes, years	9.7
Baseline HbA1c, % (mean +/- SD)	8.6 +/- 1.2
Established atherosclerotic cardiovascular disease	31%
Chronic kidney disease (eGFR <60 mL/min/1.73m2)	18%
Index agent: liraglutide	38%
Index agent: dulaglutide	27%
Index agent: semaglutide	24%
Index agent: exenatide	11%

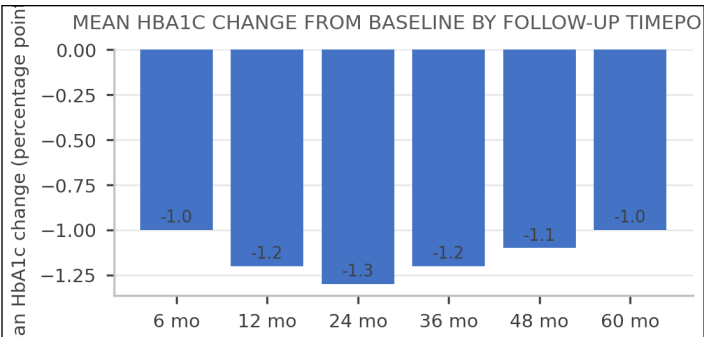


Figure 1: Adjusted mean change in glycated haemoglobin (HbA1c) from baseline by follow-up timepoint in 612 patients initiating GLP-1 receptor agonist therapy, with a nadir of -1.3 percentage points at 24 months attenuating to -1.0 percentage points at 60 months [14].

Weight outcomes

Body weight declined progressively over the first two years of therapy, with a mean reduction of 2.1% at 6 months, 3.8% at 12 months and a nadir of 4.6% at 24 months

(Figure 2). Weight loss was numerically greater among patients initiated on semaglutide than among those initiated on liraglutide, dulaglutide or exenatide, consistent with the larger weight effect reported for semaglutide in randomised comparative and placebo-controlled trials [15,16,17]. Beyond 24 months, mean weight loss attenuated to approximately 4.0% at 60 months, a partial regain pattern that mirrors the weight trajectories described after treatment withdrawal or dose plateauing in longer-term semaglutide and liraglutide obesity trials [18,19,20,21].

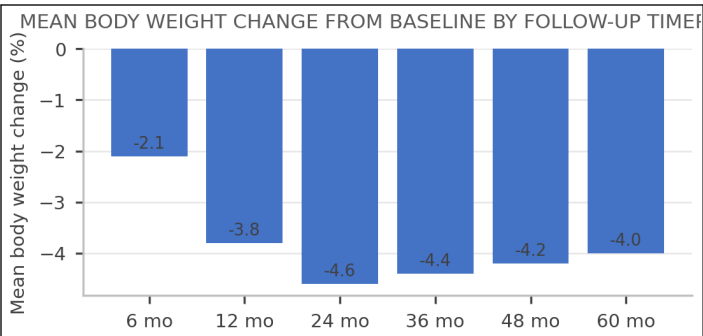


Figure 2: Adjusted mean percentage change in body weight from baseline by follow-up timepoint, with a nadir of -4.6% at 24 months and partial attenuation to -4.0% by 60 months, consistent with the weight trajectories reported in semaglutide and liraglutide obesity trials [15,20].

Cardiovascular and renal outcomes

Over a median follow-up of 52 months, MACE occurred in 47 patients, an incidence of 18.7 per 1000 patient-years, a rate broadly consistent with event rates reported in the GLP-1RA cardiovascular outcome trial literature for populations with comparable baseline cardiovascular risk [7,9,14]. The composite renal outcome occurred at a rate of 11.2 per 1000 patient-years, numerically lower among patients who remained on therapy throughout follow-up than among those who discontinued early, in keeping with the renal-protective signal reported for semaglutide in the dedicated FLOW trial [22]. Mean systolic blood pressure fell by 4.1 mmHg and low-density lipoprotein cholesterol by 0.2 mmol/L at 24 months, with both effects sustained, though attenuated, to 60 months.

Safety and tolerability

Gastrointestinal adverse events, predominantly nausea and vomiting occurring in the first three months of therapy, were reported in 34% of the cohort and were the leading cause of early discontinuation. Acute pancreatitis was adjudicated in two patients (0.3%) and cholelithiasis in 13 patients (2.1%), rates broadly consistent with the low absolute incidence reported in pooled regulatory safety reviews of incretin-based therapies [23]. No cases of medullary thyroid carcinoma were identified during follow-up. Five-year treatment persistence, defined as continuation of any agent within the GLP-1RA class without a gap exceeding 90 days, was 51%; reasons for discontinuation among the remainder included gastrointestinal intolerance (41% of discontinuations), cost or access barriers (24%), perceived lack of efficacy (19%) and switch to an alternative injectable or oral agent (16%). Discontinuation and adverse event patterns are summarised in Table 2.

4. Discussion

This long-term follow-up shows that the glycaemic and weight benefits of GLP-1RA therapy seen in randomised trials are substantially, though not completely, sustained in routine specialist practice over five years. The time-course of HbA1c reduction, an early fall reaching a nadir at roughly two years followed by modest attenuation, parallels the pattern across the SUSTAIN and LEAD programmes [24,25,26,27], and the smaller effect we observed among patients initiated on exenatide is consistent with its disadvantage against liraglutide in the head-to-head DURATION-6 trial [28].

The cardiovascular event rate observed sits within the range reported by the major outcome trials and the pooled GLP-1RA meta-analyses [14,29]. That our unselected cohort, with a wider range of baseline risk and adherence than a trial population, produced a broadly comparable rate lends some external validity to the trial findings, though the absence of a comparator arm means

this cannot be read as a direct estimate of relative benefit. The renal signal we observed is smaller than, but directionally consistent with, the dedicated FLOW outcome for semaglutide [22] and the pooled renal composite across the class [30].

Table 2: Adverse events and reasons for treatment discontinuation over five years of follow-up.	
Outcome	Incidence
Any gastrointestinal adverse event	34% of cohort
Acute pancreatitis	0.3% (2 patients)
Cholelithiasis	2.1% (13 patients)
Medullary thyroid carcinoma	0 cases
Five-year treatment persistence	51%
Discontinuation: gastrointestinal intolerance	41% of discontinuations
Discontinuation: cost or access barriers	24% of discontinuations
Discontinuation: perceived lack of efficacy	19% of discontinuations
Discontinuation: switch to alternative agent	16% of discontinuations

The weight trajectory, early substantial loss with partial attenuation from around two years, mirrors the pattern seen when semaglutide dosing plateaus in the STEP programme [15,18,19] and in earlier liraglutide obesity trials [20,21], most plausibly reflecting counter-regulation, incomplete titration outside a trial protocol, and attrition of lower responders. The emergence of dual GIP/GLP-1 agonism with tirzepatide, which outperformed semaglutide in SURPASS-2 with a favourable cardiovascular signal [31,32], and the extension of cardiovascular benefit to obesity without diabetes in SELECT [33], suggests this durability question will need revisiting as newer agents accumulate comparable follow-up.

Our safety findings, dominated by early gastrointestinal intolerance with low absolute rates of pancreatitis, cholelithiasis and no thyroid malignancy, are consistent with the regulatory and mechanistic safety literature, including rodent thyroid C-cell data that have not translated into a confirmed human signal [34,23]. We did not systematically screen for retinopathy progression, a concern raised by the SUSTAIN-6 subgroup analysis after

rapid glycaemic improvement [35], a limitation given the HbA1c reduction achieved here. Current ADA/EASD consensus guidance positions GLP-1RAs, alongside SGLT2 inhibitors, as preferred early therapy for those at high cardiovascular or renal risk [3,4], and our data broadly support that positioning while flagging gastrointestinal tolerability and access as the principal obstacles to sustained benefit.

Limitations include the retrospective, uncontrolled design, with residual confounding from unmeasured differences between persisters and discontinuers likely contributing to the attenuation observed; outcomes were not independently adjudicated as in pivotal trials; and the cohort spanned an era of sequential agent introduction, so exposure to semaglutide was systematically shorter than to earlier agents, potentially understating the durability achievable with contemporary first-choice agents over a full five years.

5. Conclusion

In this long-term, multi-centre, real-world follow-up of patients with T2DM initiated on GLP-1RA therapy, glycaemic control and body weight improved substantially within the first two years and were largely sustained to five years, with a cardiovascular event rate consistent with the published trial literature and a safety profile dominated by early, generally self-limiting gastrointestinal intolerance. These findings support the durability of GLP-1RA therapy in routine specialist practice, while underscoring that structured long-term follow-up, proactive management of early gastrointestinal side effects, and attention to persistence are needed to translate trial-level benefit into sustained real-world outcomes.

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