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COMPARATIVE EFFECTIVENESS OF GLP-1 RECEPTOR AGONISTS VERSUS CONVENTIONAL ANTI-DIABETIC THERAPY ON GLYCEMIC CONTROL AND WEIGHT REDUCTION: A RETROSPECTIVE COHORT STUDY OF PATIENTS WITH TYPE 2 DIABETES

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ABSTRACT

Background: Management of type 2 diabetes mellitus (T2DM) requires effective glycemic control while limiting weight gain, which remains a challenge with conventional oral regimens. Real-world comparative data on glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are limited.

Objective: To compare the 12-month effectiveness of GLP-1 RAs and conventional antidiabetic therapy on glycated hemoglobin (HbA1c) and body weight in adults with T2DM.

This retrospective cohort study used patient data. Patients receiving a GLP-1 RA or conventional antidiabetic therapy were matched 1:1 by propensity score (age, sex, diabetes duration, baseline HbA1c, and baseline BMI), yielding two cohorts of 170 patients each (N = 340). Primary outcomes were the changes in HbA1c and body weight from baseline to 12 months. Secondary outcomes were the proportions of patients achieving HbA1c < 7.0% and a weight reduction of ≥ 5%.

Results: Baseline characteristics were balanced after matching. At 12 months, the GLP-1 RA cohort had a greater reduction in HbA1c (−1.55% vs −1.00%; $p < 0.001$) and greater weight loss (−6.00 kg vs −1.60 kg; $p < 0.001$). A higher proportion of patients in the GLP-1 RA cohort achieved HbA1c < 7.0% (55.9% vs 21.2%; $p < 0.001$) and weight loss of ≥ 5% (85.3% vs 1.2%; p
< 0.001).

Conclusion: In this real-world cohort, GLP-1 RA therapy was associated with greater glycemic improvement and weight reduction than conventional antidiabetic therapy over 12 months. Prospective studies are needed to confirm these findings.

KEYWORDS: GLP-1 receptor agonists; type 2 diabetes mellitus; propensity score matching; real-world evidence; retrospective cohort study; weight loss

INTRODUCTION

Progressive loss of beta-cell function, peripheral insulin resistance, and chronic hyperglycemia remains the hallmarks of type 2 diabetes mellitus (T2DM), which continues to be a major public health issue (American Diabetes Association Professional Practice Committee, 2024; Davies et al., 2022). While the prevalence of metabolic disease keeps growing, the cost of the disease to the health care system is high and there is a need for actions other than improving glycemic control to improve cardiometabolic health. Conventional pharmacotherapy, primarily metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors and insulin, has proved to be effective in lowering blood glucose levels, but has also been associated with weight gain as part of the treatment, failure of treatment, and hypoglycemia (Buse et al., 2020; Davies et al., 2022).

Excess body weight is not just a risk factor for insulin resistance; it also predisposes cardiovascular complications, and therapies that lead to weight loss along with glycemic control are clinically valid (Davies et al., 2022).

The incretin mimetics (glucagon-like peptide-1 receptor agonists [GLP-1 RAs]) promote glucose-dependent insulin secretion, suppress the secretion of postprandial glucagon, slow gastric emptying, and inhibit central pathways of appetite (Drucker, 2018). They do not cause hypoglycemia (insulotropic effect is glucose dependent) and decrease HbA1c and body weight. These glycemic, weight-loss and cardiovascular benefits have been proven in large randomized controlled trials (Gerstein et al., 2019; Marso et al., 2016a, 2016b; Pratley et al., 2018).

Randomized trials, however, are conducted with good study design and strict inclusion and adherence criteria; they may not represent actual clinical practice.

Very little data exists comparing the effectiveness of GLP-1 RAs to conventional therapy in usual care. Demographic characteristics, adherence to treatment, polypharmacy, and comorbidities vary in real world populations compared to trial populations. Conventional agents are also still prescribed widely, due to being cheaper to obtain and long-term use in clinical practice. Head-to-head, real-world comparisons are thus required to support clinical decisions and health care policy choices, while longer-term real-world data will prove useful for clinicians and health care policymakers.

This is a retrospective cohort study to compare the 12-month effectiveness of GLP-1 RA therapy versus conventional antidiabetic therapy for glycemic control and body weight in adults with T2DM in the real-world setting with the use of propensity score matching to minimize confounding. In our hypothesis, the patients receiving GLP-1 RAs for 12 months would have more reduction in HbA1c and body weight as compared to the conventional therapy group.

LITERATURE REVIEW

The management of T2DM has shifted from a glucose-centered to a more holistic approach to reduce the cardiovascular risk, preserve renal function and control excess body weight over the last 20 years (Buse et al., 2020; Davies et al., 2022). Worldwide, treatment algorithms have focused on the use of metformin as first-line treatment for hyperglycemia, and sulfonylureas, thiazolidinediones, DPP-4 inhibitors, or insulin are used as needed (Davies et al., 2022). While these methods help to reduce blood sugar levels in the short term, they may not be effective over the long term due to loss of effectiveness over time, side effects, and safety risks.

Treatment-emergent hypoglycemia and weight gain are associated with sulfonylureas and insulin. In addition, sulfonylureas can stimulate the production of endogenous insulin in a glucose independent fashion, which can produce anabolism (lipogenesis) of lipids, and exogenous insulin can also cause weight gain (from a reduction in glucosuria and some hepatic lipogenesis). Hyper adiposity, and especially visceral adiposity is associated with insulin resistance in the periphery, low-grade systemic inflammation and may negate metabolic advantages of glycemic control. Even when treated with standard therapy, beta-cell function has reduced over time and secondary failure occurred as well as an increase in the use of multiple medications over time (as seen in the long-term studies, such as the United Kingdom Prospective Diabetes Study (UKPDS)) (Turner et al., 1999).

In T2DM, the incretin effect is absent, and GLP-1 is an incretin hormone released from L-cells of the intestine when there is food. It acts via G-protein coupled receptors in the pancreas, CNS, and gastrointestinal tract (Drucker, 2018). There are GLP-1 RAs, which mimic the endogenous hormone, which enhances glucose-dependent insulin secretion from beta-cells and inhibits glucagon secretion from alpha-cells. Hypoglycemia is unlikely to occur with GLP-1 RAs as monotherapy or in combination with other non-hypoglycemic medications but can be a risk when using them in combination with insulin and/or sulfonylureas (Davies et al., 2022).

In addition to glycemic control, GLP-1 RAs have extra pancreatic effects, which lead to loss of weight. They inhibit the gastric emptying rate, thus helping to regulate glucose levels after meals, and they have direct or indirect activity on GLP-1 receptors in the hypothalamic arcuate nucleus and brainstem (nucleus of the solitary tract and area postrema) to increase satiety and reduce hunger (Drucker, 2018; Nauck et al., 2021). This decrease in food consumption and calories results in consistent weight loss.

The clinical efficacy of GLP-1 RAs has been proven in large, randomized trial programs like SUSTAIN (Marso et al., 2016b; Pratley et al., 2018), AWARD (Dungan et al., 2014) and PIONEER (Rosenstock et al., 2019). In these studies, GLP-1 RAs achieved a substantial HbA1c reduction compared to placebo and several other active comparators as well as lost about 3–6+ kg (Pratley et al., 2018; Nauck et al., 2021). For adults who are overweight or obese (but not diabetic), once a week semaglutide has been shown to result in significantly more weight loss than placebo (Wilding et al., 2021). There are also cardiovascular outcome trials and meta-analyses that have demonstrated decreases in major adverse cardiovascular events for some GLP-1 RAs (Gerstein et al., 2019; Kristensen et al., 2019; Marso et al., 2016a; Sattar et al., 2021).

Even with this evidence, results of trials are challenging to transfer to routine care. Eligibility criteria are strict and clinical contact regular, dose titration in line with protocol, and adherence regularly checked, with the result that elderly people or individuals with complex multimorbidity/polypharmacy are underrepresented, lower socio-economic status individuals, and variable adherence. These differences might impact glycemic and weight changes that may be seen in clinical practice. Current real-life observational studies have been done, but results have been varied, and gastrointestinal intolerance and early discontinuation were proposed as explanations for the differences between real-life and phase 3 studies, as well as baseline patient characteristics that are different from those in the phase 3 studies (Tan et al., 2024; Weiss et al., 2020). Moreover, some studies of comparative effectiveness in the real world follow patients for only 6 months or shorter (Lingvay et al., 2020), and administrative claims studies have a risk of miscoding and lack clinical detail (Tan et al., 2024).

Multiple direct, longer-term (12-months) real-world comparisons of GLP-1 RA initiation with diabetes patients with intensified conventional therapy are thus warranted, as this therapy is widely used as add-on therapy due to its lower acquisition cost and familiarity. Since the marked glycemic and weight decreasing effect of GLP-1 RAs can be helpful to inform clinicians, endocrinologists, and health care decisionmakers, it is important to determine whether

these effects are sustained over 12 months of routine care, after adjusting for important confounding factors using PSM.

Objectives

The main goal was to evaluate the long-term (12 months) real-world efficacy of GLP-1 RA therapy versus conventional antidiabetic treatment in adults with T2DM on glycemic control and body weight. The objectives were:

1. To compare absolute change in HbA1C levels from baseline to 12 months of treatment between propensity score-matched patients who started GLP-1 RAs and those who started conventional antidiabetic agents.
2. To compare the absolute reduction in body weight and body mass index (BMI) from baseline to 12 months in the two matched groups.
3. To compare the proportion of patients getting HbA1c < 7.0% at 12 months in each group.
4. To compare the percentage of patients in each group who achieved weight loss ≥ 5% for 12 months.

Research Hypotheses

The following hypotheses were developed based on the theoretical framework and on the available evidence. All testing was done two-tailed, but a more beneficial effect of GLP-1 RA therapy was hypothesized.

Primary hypothesis #1 (glycemic control). No difference in the mean of HbA1c level at 12 months between GLP-1 RA and conventional therapy groups (H0). H1: There is a difference in the mean change in HbA1c at 12 months between the groups (a larger decrease in HbA1c was expected with GLP-1 RA therapy).

Primary hypothesis 2 (weight). The null hypothesis is that the means of the change in body weight at 12 months are equal for the two groups. Outcome: At 12 months, the mean change in body weight was found to be different between the groups (weight loss expected in GLP-1 RA group).

Secondary hypothesis 3a. H0: There is no difference between the groups in the proportion of patients with HbA1c < 7.0% at 12 months. There is a difference in the proportions of the groups.

Secondary hypothesis 3b. The null hypothesis for this test is that at 12 months the proportions of patients with weight loss ≥ 5% in each group is equal. There are differences in the ratios across the groups.

Theoretical and Conceptual Framework

The research is focused on the pathophysiological mechanisms of the incretin axis, and on cross pathway interactions between excess adiposity, peripheral insulin resistance and beta-cell dysfunction in T2DM. Glucose lowering is not the sole target for persistent glycemic control and cardiometabolic risk reduction may be best achieved via a strategy that involves targeting central appetite regulation, slowing nutrient absorption and re-establishing glucose-dependent endocrine responses.

The action of conventional pharmacotherapy is at the periphery, or it causes stimulation of the pancreas, but has no effect on the basic physiology. Sulfonylureas block ATP-sensitive potassium (K-ATP) channels in the beta cells of the pancreas and induce exocytosis of pre-formed granules without regard to the level of plasma glucose. This will lower blood glucose, though there will still be a risk of hypoglycemia, and will increase anabolic lipogenesis.

Systemic insulin (exogenous insulin) inhibits lipolysis in adipose tissue and stimulates deposition of fatty acids in adipose tissue, leading to weight gain. In turn, the resulting visceral adiposity causes low-grade chronic inflammation by the infiltration of macrophages and changes in the secretion of adipokines and dysregulates insulin receptor substrate signaling in tissues such as skeletal muscle and liver. Insulin secretagogues and exogenous insulin can thus create a vicious cycle of increasing insulin resistance because of treatment of hyperglycemia.

The incretin paradigm seeks to restore the incretin effect that is greatly lost in T2DM. After food consumption, GLP-1 is secreted by the enteroendocrine L-cells, which bind to its G-protein coupled receptor (GLP-1R) to activate intracellular signaling pathways resulting in an increase in insulin secretion only when glucose levels are elevated. The signal diminishes with the return of normal glucose, thus giving intrinsic protection against hypoglycemia. Upon activation, GLP-1 causes a reduction in the level of glucagon in the alpha-cells, resulting in a reduction of the liver's glucose production, also maintaining the glucagon response to hypoglycemia.

Extra pancreatic effects of GLP-1 RAs are also possible. They inhibit the brainstem and hypothalamic arcuate nucleus (ARC) neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons, as well as activating pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons, which promotes feelings of satiety, decreases food reward, and reduces energy intake (Drucker, 2018). Peripheral delayed gastric emptying helps moderate postprandial hyperglycemia and prolong satiety. The dual central and peripheral physiological model is a concept that can be compared to conventional therapy – from the glucose-lowering approach to a return of incretin signaling and satiety and induction of weight loss.

METHODS

This was a retrospective cohort study based on existing patient data.

Study population

Eligible adults were those with T2DM who initiated GLP-1 RA therapy or who increased their diabetes medication use with conventional antidiabetic medications. Baseline and 12-month HbA1c and body weight measurements had to be available in the patients. Eligible patients were subsequently matched 1:1 on the basis of the propensity score,

described below, which resulted in 170 patients for each group.

Exposure groups

The GLP-1 RA group received GLP-1 receptor agonist therapy, while the conventional therapy group used conventional antidiabetic agents (metformin, sulfonylureas, DPP-4 inhibitors, or insulin). The index date was the date of therapy initiation, and patients were analyzed based on the therapy they initiated.

Data Collection

Baseline and 12-month follow-up data were recorded for age, sex, duration of diabetes, HbA1c, weight and height (for BMI). Adherence and persistence to medication were assessed using prescription refill records.

The primary outcomes were the absolute changes in HbA1c and body weight from baseline to 12 months. Secondary outcomes included the change in BMI, percentage of patients with HbA1c < 7.0% at 12 months and percentage of patients with weight loss ≥ 5% from baseline.

Statistical analysis

Shapiro-Wilk tests, normal Q-Q plots, and histograms were used to test continuous variables for normality. Data are expressed as mean ± SD (standard deviation) for variables with a normal distribution and as median and interquartile range for those that do not have a normal distribution. Categorical variables are displayed in the form of frequencies and percentages.

To reduce confounding indication in this retrospective observational study, patients were matched without replacement using the propensity score, 1:1. Propensity scores were derived from a multivariable logistic regression model that contained the following factors: age, sex, duration of diabetes, baseline HbA1c, and baseline BMI. The covariate balance was assessed using standardized mean differences (SMD), defined as being within a range of < 0.1 considered ideal and < 0.2 acceptable balance. Independent-samples t tests were used to compare baseline characteristics between groups for continuous variables, while chi-square tests were used for categorical variables.

Changes within the groups at 12 months after baseline were compared using paired Student t-tests (normally distributed variables) or Wilcoxon signed-rank tests (skewed variables).

Independent-samples t tests were used to make between-group comparisons of the primary continuous outcomes (change in HbA1c and body weight). Categorical outcome comparisons were made with Pearson chi-square tests; if frequency counts in the cells were less than 5, Fisher exact tests were used. Patients whose data were missing at baseline or at 12 months for HbA1c and body weight were not included in the analysis (complete-case analysis). The effect sizes are presented with 95% confidence intervals (CI). All tests were performed two-sided and the significance level set at $p < 0.05$. Data was analyzed with IBM SPSS Statistics.

RESULTS

Study population

After 1:1 propensity score matching, 340 patients (170 patients in the GLP-1 RA group and 170 patients in the conventional therapy group) were analyzed. There were no significant differences between baseline characteristics of the matched groups (Table 1). Standardized mean differences of all matching covariates were ≤ 0.12 (based on the values listed in Table 1) and thus were deemed to be acceptable for covariate balance.

Baseline characteristics

The mean age in the group receiving GLP-1 RA and conventional therapy was 53.8 and 54.2 years, respectively. The average duration of T2DM was 6.5 and 6.7 years, respectively. Mean baseline glycated hemoglobin (HbA1c) levels (8.5% vs 8.6%) and mean baseline body weight and BMI (Table 1) were not different.

Table 1. Baseline characteristics of the propensity score-matched cohorts

Characteristic	GLP-1 RA (n = 170)	Conventional therapy (n = 170)	p-value
Age (years)	53.8 ± 6.9	54.2 ± 7.1	0.582
Sex, female / male, n (%)	92 (54.1) / 78 (45.9)	89 (52.4) / 81 (47.6)	0.748
Diabetes duration (years)	6.5 ± 2.2	6.7 ± 2.4	0.415

Baseline HbA1c (%)	8.5 ± 0.8	8.6 ± 0.9	0.279
Baseline weight (kg)	90.5 ± 11.8	91.2 ± 12.4	0.594
Baseline BMI (kg/m²)	32.8 ± 4.2	33.1 ± 4.5	0.521

Values are mean ± SD unless otherwise stated. BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin.

Glycemic and weight outcomes

At 12 months, both groups improved, but the improvement was greater with GLP-1 RAs. Mean HbA1c fell by 1.55 percentage points in the GLP-1 RA group (from 8.50% to 6.95%) and by 1.00 percentage point in the conventional therapy group (from 8.60% to 7.60%); the between-group difference in HbA1c change was −0.55 percentage points (95% CI −0.62 to −0.48; $p < 0.001$;
Table 2).

Body weight decreased by 6.00 kg (BMI −2.20 kg/m²) in the GLP-1 RA group, compared with 1.60 kg (BMI −0.58 kg/m²) in the conventional therapy group. The between-group difference in weight change was −4.40 kg (95% CI −4.65 to −4.15; $p < 0.001$; Table 2).

Table 2. Change from baseline to 12 months in HbA1c, body weight, and BMI

Outcome	**GLP-1 RA (n = 170)**	**Conventional therapy (n = 170)**	**Between-group difference (95% CI)**	**p-value**
Baseline HbA1c (%)	8.50 ± 0.80	8.60 ± 0.90	—	0.279
12-month HbA1c (%)	6.95 ± 0.72	7.60 ± 0.75	−0.65 (−0.81 to −0.49)	< 0.001
HbA1c change (%)	−1.55 ± 0.35	−1.00 ± 0.35	−0.55 (−0.62 to −0.48)	< 0.001
Baseline weight (kg)	90.50 ± 11.80	91.20 ± 12.40	—	0.594

12-month weight (kg)	84.50 ± 11.50	89.60 ± 12.50	−5.10 (−7.66 to −2.54)	< 0.001
Weight change (kg)	−6.00 ± 1.40	−1.60 ± 0.85	−4.40 (−4.65 to −4.15)	< 0.001
BMI change (kg/m²)	−2.20 ± 0.50	−0.58 ± 0.30	−1.62 (−1.71 to −1.53)	< 0.001

Values are mean ± SD. Negative values indicate a reduction from baseline. Between-group differences are GLP-1 RA minus conventional therapy; baseline p-values are as in Table 1.

Target attainment

At 12 months, HbA1c < 7.0% was achieved by 95 patients (55.9%) in the GLP-1 RA group and 36 patients (21.2%) in the conventional therapy group ($p < 0.001$). A weight reduction of ≥ 5% from baseline was achieved by 145 patients (85.3%) in the GLP-1 RA group and 2 patients (1.2%) in the conventional therapy group ($p < 0.001$) (Table 3).

Table 3. Proportions of patients achieving glycemic and weight targets at 12 months

Outcome	GLP-1 RA, n (%)	Conventional therapy, n (%)	Difference (95% CI)	p-value
HbA1c < 7.0%	95 (55.9)	36 (21.2)	34.7 points (25.0 to 44.4)	< 0.001
Weight reduction ≥ 5%	145 (85.3)	2 (1.2)	84.1 points (78.6 to 89.7)	< 0.001

DISCUSSION

In this retrospective, propensity score-matched study of adults with T2DM, GLP-1 RA therapy led to more favorable changes in HbA1c and body weight for 12 months compared with conventional antidiabetic therapy, and a higher percentage of patients with HbA1c < 7.0% and body weight loss ≥ 5%. The findings support our hypotheses and indicate a possible clinical benefit of GLP-1 RA therapy in appropriate patients; however, the study's observational design does not allow causal inferences.

The reduction in the HbA1c was about 1.5 times higher in the GLP-1 RA group (HbA1C reduction, −1.55%) than in the conventional group (HbA1C reduction, −1.00%). This follows the trend of randomized controlled trials of GLP-1 RAs (Pratley et al., 2018). In AWARD-6, HbA1c was reduced by 1.42% with dulaglutide, and by 1.36% with liraglutide at 26 weeks (Dungan et al., 2014); and in PIONEER 3, HbA1c was reduced an additional 0.5 percentage points with oral semaglutide 14 mg compared to sitagliptin, after 26 weeks (Rosenstock et al., 2019). There is a between-group difference of a similar magnitude in our study (−0.55 percentage points), but with longer follow-up (12 months), indicating that the benefit also occurs in the real clinical setting.

The effect sizes may vary between an observational setting and a trial setting because of differences in adherence and suboptimal titration and baseline glycemic profile. There is a plausible explanation for the greater glycemic effect due to glucose-dependent insulin secretion and suppression of glucagon after the meal; there is a low intrinsic risk of hypoglycemia (Drucker, 2018).

The groups had the greatest difference regarding weight loss, with patients receiving GLP-1 RAs losing a mean of 6.00 kg and 85.3% of them losing at least 5% of body weight, while conventional therapy resulted in very little weight loss. The difference in weight change between the groups (−4.40 kg) was greater than the difference between

oral semaglutide 14 mg and sitagliptin in PIONEER 3 (Rosenstock et al., 2019) and the mean weight loss with the use of oral semaglutide 14 mg was higher than that with dulaglutide (2.9 kg) and liraglutide (3.6 kg) in AWARD-6 (Dungan et al., 2014). Treatment can include intensified treatment (sulfonylureas and insulin) which are known to cause weight gain which increases insulin resistance and cardiometabolic risk (Davies et al., 2022). Weight loss induced by GLP-1 RAs is probably due to delayed gastric emptying and central appetite suppression, both of which result in a reduction of energy intake (Drucker, 2018). Again, this is consistent with previous reports of increased weight loss when using higher dose of semaglutide in adults with overweight or obesity that do not have diabetes (Wilding et al., 2021), though a different population.

Our results are in line with previous real-world studies. HbA1c reductions with once weekly GLP-1 RAs at 12 months were like the ones observed by Tan et al. (−1.5% vs. −1.0%) in adults with T2DM in the USA, while weight loss was greater with GLP-1 RAs in our cohort. Similarly, patients who intensified with a GLP-1 RA had higher odds of achieving HbA1c < 7.0% than those who intensified with oral agents (odds ratio 1.35) or insulin (odds ratio 1.77) after 180 days, in propensity score-matched US cohorts (Lingvay et al., 2020). Less evidence is available for South Asia. The retrospective cohort consisted of 624 Pakistani patients who initiated liraglutide, with mean HbA1c reduction of 1.45 percentage points and weight reduction of 7.51 kg after 24 months, with only 27.2% of patients experiencing a weight loss of ≥ 5% at 24 months (Butt et al., 2024). The percentage of patients with HbA1c reduction greater than or equal to 5% was similar in our GLP-1 RA group, while a significantly higher proportion of patients in our cohort (85.3%) had a greater than or equal to 5% reduction. The same study was conducted with liraglutide alone, rather than with a comparison group of conventional therapy, and with varying
definitions of follow-up and target, making it difficult to compare with other studies. The percentages of our GLP-1 RA patients losing ≥ 5% of their weight were also higher than in the US GLP-1 RA cohort (26.7%, Tan et al., 2024); this finding should be taken with a grain of salt.

Although not covered in this study, glycemic control and weight loss decreased the long-term risk of microvascular and macrovascular complications (Davies et al., 2022). Conventional oral agents remain in use as intensification agents, because of their low cost and common knowledge by prescribers. The results of this study suggest that GLP-1 RAs may be more beneficial for glycemic and weight control, but the benefits of earlier GLP-1 RA use on long-term disease outcomes and health care utilization should be explored in studies that assess these outcomes.

Findings are of clinical significance

In addition to statistical significance, the amount of difference observed is important for clinical practice. The between-group difference in HbA1c change was −0.55 percentage point, and the mean 12-month HbA1c level in the GLP-1 RA group was 6.95%, versus 7.60% in the conventional therapy group. The absolute difference was 34.7 percentage points (about one additional patient to reach HbA1c < 7.0% for every three treated) with 55.9% of patients in the GLP-1 RA group having HbA1C < 7.0% versus 21.2% in the conventional therapy group. The mean difference for body weight was −4.40 kg, which was equivalent to a BMI difference of
−1.62 kg/m², and the absolute difference in the proportion of patients who experienced a weight loss of at least 5% of their baseline weight was 84.1 percentage points.

These data provide descriptive summaries of this cohort and cannot be interpreted as treatment effects that would be observed if this cohort were duplicated elsewhere, as differences in patients that are not measured may persist. They also highlight patients who have completed 12-month measurements, and patients who do not have measurements were not included. Further, the GLP-1 RA group had a low standard deviation of weight change (1.40 kg), suggesting that the response of the patients was relatively even. Individual responses to GLP-1 RAs in routine care can differ, and replication in other datasets is therefore warranted.

It is important to consider safety, tolerability, and adherence considerations. Safety, tolerability, and adherence considerations are important.

Effectiveness from this study is not analyzed in terms of safety and tolerability, but this is an important consideration for the extent to which the effectiveness observed here can be maintained in routine care. A gastrointestinal adverse event is a commonly reported tolerability issue with GLP-1 RAs; for instance, in the AWARD-6 trial, nausea was reported in 20% of dulaglutide recipients and 18% of liraglutide recipients, with a rate of 0.34 and 0.52 events per patient per year, respectively, and no severe hypoglycemia reported (Dungan et al., 2014).

Another issue to consider in daily practice is the use of persistence with treatment. Of those who initiated an injectable GLP-1 RA, 47.7% stopped by 12 months and 70.1% by 24 months in a claims-based study in the USA, with adherence higher for weekly GLP-1 RAs than daily GLP-1
RAs (Weiss et al., 2020). It is not possible to say whether there were differences in persistence between the two groups in the present study because adherence was not reported but was evaluated using prescription refill records. The observed effects might have been caused by variations in adherence, dose, and adverse events, which should be reported in future analyses in addition to HbA1c and weight.

The practice implications for the South Asian

The results also apply to diabetes care in Pakistan and beyond in South Asia, where there is limited real-world experience with GLP-1 RAs (Butt et al., 2024). Conventional agents have low costs and are known by the prescriber

and continue to be utilized. However, GLP-1 RAs cost more and a greater drop in HbA1c or body weight has not been proven to be of good value. The GLP-1 RAs are, therefore, a reasonable first choice for patients with a specific weight reduction goal, who also can afford to maintain treatment, and may be considered for patients in whom maintaining treatment is more of a focus. For patients who have a specific weight reduction treatment goal and can sustain treatment, GLP-1 RAs can be considered a reasonable first choice and may be considered by formulary committees in weighing the benefits against acquisition costs.

These results would need to be translated to local cost-effectiveness analyses before they could be used to inform procurement/reimbursement. Here, the analyses would require reflecting complexities, hospital utilization, and the cost of medicines used in the long run, which were not accounted for. Regional or multi-center studies in Pakistan would also be helpful to address the applicability of the effect sizes seen in this cohort to patients with other clinical characteristics and access to health care.

The results have practical implications for individual selection of treatment. A combined glycemic and weight benefit is most important for the patient group with elevated baseline HbA1c and BMI, for whom a combined benefit is likely most important, and which is the target population for this cohort (HbA1c baseline of approximately 8.5% and BMI baseline of approximately 33 kg/m2). Periodic measurement of HbA1c and weight (at 12 months, as in this study) can help the clinician determine if the desired result is being attained and adjust the therapy, dose, or adherence support as needed. The above remarks are relevant to the patients examined and should not be extrapolated to patients with similar characteristics than those studied without additional evidence.

LIMITATIONS

The benefits are that the key demographic and clinical covariates were accounted for using propensity score matching, which helps to reduce selection bias, and that the effects measured were persistent rather than transient, due to using the complete 12-month follow-up. The results were discussed in the context of the following limitations:

The retrospective design relies on completeness and accuracy of data recorded

Only measured covariates are balanced by propensity score matching. Because of the potential for unmeasured confounders, including diet, physical activity, use of over-the-counter medications, and socioeconomic status, that could have impacted access to the GLP-1 RAs (which are more expensive) and outcomes, residual confounding by indication is possible.

Comorbidities, renal function, and previous glucose lowering therapy were not included in the propensity score model.

These two groups are potentially heterogeneous for dose, agent and combination therapy, making it challenging to come to agent-specific conclusions.

Prescription refill information was used to determine adherence. The differences were observed and could have been affected by treatment discontinuation and/or switching during follow-up as these were not modeled separately.

The duration of effects and safety and tolerability could not be evaluated as only 12-month follow-up was conducted.

The results of this retrospective cohort study may not be representative of other health care populations or health care settings because they were derived from routine-care data.

Future research directions

This study has several implications for future research. First, prospective studies or randomized trials comparing specific GLP-1 RAs with specific conventional agents are needed to confirm the observations herein and establish whether any differences are agent-specific. Second, it would be important to see if the HbA1c and weight changes persist after 12 months and if the weight loss is associated with fewer complications. Third, adverse events, discontinuation of treatment, switching to another treatment, and dose should be recorded for future research to be able to evaluate the effectiveness along with tolerability and persistence.

Fourth, analyses should be adjusted for a broader range of covariates (not included in the current propensity score model, such as comorbidities, renal function, concomitant medication, and prior therapy) and sensitivity analyses should be performed to determine the degree of unmeasured confounding needed to explain the observed differences. Fifth, patient reported outcomes (PARs) (treatment satisfaction, quality of life, etc.) would be included in studies that would demonstrate the added value of weight loss to the patient. In summary, clinical trials in other South Asian contexts with cost analysis would enable decisionmakers to determine the most cost-effective way to use GLP-1 RAs.

CONCLUSION

In real-world adult T2DM population, matched various propensities, GLP-1 receptor agonists resulted in greater HbA1c and weight loss than conventional antidiabetic therapies after 12 months. These results support the use of GLP-1 RAs for the treatment of glycemic dysfunction

and excess adiposity in the clinical setting. More long-term studies with safety and cost information are required to validate these conclusions.

Clinical Implications

For this, and based on the current guidance of the American Diabetes Association Professional Practice Committee (2024) and Davies et al (2022), the following should be considered for outpatient diabetes management:

1. For patients with T2DM with elevated baseline HbA1c and overweight or obese, consider using GLP-1 RAs as part of treatment, if cost-effective and accessible.
2. Periodic monitoring of HbA1c and BMI as part of a multidisciplinary diabetes care team to inform dose titration, and help achieve adherence, at regular intervals (e.g. at 6 months, 12 months as in this study, etc.).
3. Due to the lack of cost of medications and lack of long-term outcomes, health care administrators and formulary committees should take into account the long-term cost-effectiveness and clinical benefit of GLP-1 RAs, including different access options.

REFERENCES

1. American Diabetes Association Professional Practice Committee. (2024). 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2024. Diabetes Care, 47(Suppl. 1), S158–S178. https://doi.org/10.2337/dc24-S009
2. Buse, J. B., Wexler, D. J., Tsapas, A., Rossing, P., Mingrone, G., Mathieu, C., D'Alessio, D. A., & Davies, M. J. (2020). 2019 update to: Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care, 43(2), 487–493. https://doi.org/10.2337/dci19-0066
3. Butt, M. D., Ong, S. C., Rafiq, A., Batool, N., Saifi, R., Yaseen, S., Kaukab, I., & Ramzan, B. (2024). Long-term clinical efficacy of liraglutide for type 2 diabetes: Real-world evidence and outcomes from Pakistan. Journal of Pharmaceutical Policy and Practice, 17(1), Article 2432462. https://doi.org/10.1080/20523211.2024.2432462
4. Davies, M. J., Aroda, V. R., Collins, B. S., Gabbay, R. A., Green, J., Maruthur, N. M., Rosas, S. E., Del Prato, S., Mathieu, C., Mingrone, G., Rossing, P., Tankova, T., Tsapas, A., & Buse, J. B. (2022). Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care, 45(11), 2753–2786. https://doi.org/10.2337/dci22-0034
5. Drucker, D. J. (2018). Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metabolism, 27(4), 740–756. https://doi.org/10.1016/j.cmet.2018.03.001
6. Dungan, K. M., Povedano, S. T., Forst, T., González, J. G. G., Atisso, C., Sealls, W., & Fahrbach, J. L. (2014). Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): A randomised, open-label, phase 3, non-inferiority trial. The Lancet, 384(9951), 1349–1357. https://doi.org/10.1016/S0140-6736(14)60976-4
7. Gerstein, H. C., Colhoun, H. M., Dagenais, G. R., Diaz, R., Lakshmanan, M., Pais, P., Probstfield, J., Riesmeyer, J. S., Riddle, M. C., Rydén, L., Xavier, D., Atisso, C. M., Dyal, L., Hall, S., Rao-Melacini, P., Wong, G., Avezum, A., Basile, J., Chung, N., . . . REWIND Investigators. (2019). Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): A double-blind, randomised placebo-controlled trial. The Lancet, 394(10193), 121–130. https://doi.org/10.1016/S0140-6736(19)31149-3
8. Kristensen, S. L., Rørth, R., Jhund, P. S., Docherty, K. F., Sattar, N., Preiss, D., Køber, L., Petrie,
9. M. C., & McMurray, J. J. V. (2019). Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. The Lancet Diabetes & Endocrinology, 7(10), 776–785. https://doi.org/10.1016/S2213-8587(19)30249-9
10. Lingvay, I., Desouza, C., Kirk, A. R., Mangla, K. K., & Wolden, M. L. (2020). Real-world clinical outcomes following treatment intensification with GLP-1 RA, OADs or insulin in patients with type 2 diabetes on two oral agents (PATHWAY 2-OADs). BMJ Open Diabetes Research & Care, 8(2), Article e001830. https://doi.org/10.1136/bmjdrc-2020-001830
11. Marso, S. P., Daniels, G. H., Brown-Frandsen, K., Kristensen, P., Mann, J. F. E., Nauck, M. A., Nissen, S. E., Pocock, S., Poulter, N. R., Ravn, L. S., Steinberg, W. M., Stockner, M., Zinman, B., Bergenstal, R. M., & Buse, J. B. (2016a). Liraglutide and cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine, 375(4), 311–322. https://doi.org/10.1056/NEJMoa1603827
12. Marso, S. P., Bain, S. C., Consoli, A., Eliaschewitz, F. G., Jódar, E., Leiter, L. A., Lingvay, I., Rosenstock, J., Seufert, J., Warren, M. L., Woo, V., Hansen, O., Holst, A. G., Pettersson, J., Vilsbøll, T., & SUSTAIN-6 Investigators. (2016b). Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. New England Journal of Medicine, 375(19), 1834–1844. https://doi.org/10.1056/NEJMoa1607141
13. Nauck, M. A., Quast, D. R., Wefers, J., & Meier, J. J. (2021). GLP-1 receptor agonists in the treatment of type 2 diabetes—State-of-the-art. Molecular Metabolism, 46, Article 101102. https://doi.org/10.1016/j.molmet.2020.101102
14. Pratley, R. E., Aroda, V. R., Lingvay, I., Lüdemann, J., Andreassen, C., Navarria, A., Viljoen, A., & SUSTAIN 7 Investigators. (2018). Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): A randomised, open-label, phase 3b trial. The Lancet Diabetes & Endocrinology, 6(4), 275–286.

https://doi.org/10.1016/S2213-8587(18)30024-X
15. Rosenstock, J., Allison, D., Birkenfeld, A. L., Blicher, T. M., Deenadayalan, S., Jacobsen, J. B., Serusclat, P., Violante, R., Watada, H., Davies, M., & PIONEER 3 Investigators. (2019). Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: The PIONEER 3 randomized clinical trial. JAMA, 321(15), 1466–1480. https://doi.org/10.1001/jama.2019.2942
16. Sattar, N., Lee, M. M. Y., Kristensen, S. L., Branch, K. R. H., Del Prato, S., Khurmi, N. S., Lam,
17. C. S. P., Lopes, R. D., McMurray, J. J. V., Pratley, R. E., Rosenstock, J., & Gerstein, H. C. (2021). Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of randomised trials. The Lancet Diabetes & Endocrinology, 9(10), 653–662. https://doi.org/10.1016/S2213-8587(21)00203-5
18. Tan, X., Divino, V., Amamoo, J., Xie, L., Coyle, K. B., Gamble, C. L., Guevarra, M., Paprocki, Y., & King, A. A. (2024). Real-world effectiveness of once-weekly glucagon-like peptide-1 receptor agonists (OW GLP-1RAs) in comparison with dipeptidyl peptidase-4 inhibitors (DPP-4is) for glycemic control and weight outcomes in type 2 diabetes mellitus (RELATE). Clinical Drug Investigation, 44(4), 271–284. https://doi.org/10.1007/s40261-024-01354-2
19. Turner, R. C., Cull, C. A., Frighi, V., & Holman, R. R. (1999). Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: Progressive requirement for multiple therapies (UKPDS 49). JAMA, 281(21), 2005–2012. https://doi.org/10.1001/jama.281.21.2005
20. Weiss, T., Carr, R. D., Pal, S., Yang, L., Sawhney, B., Boggs, R., Rajpathak, S., & Iglay, K. (2020). Real-world adherence and discontinuation of glucagon-like peptide-1 receptor agonists therapy in type 2 diabetes mellitus patients in the United States. Patient Preference and Adherence, 14, 2337–2345. https://doi.org/10.2147/PPA.S277676
21. Wilding, J. P. H., Batterham, R. L., Calanna, S., Davies, M., Van Gaal, L. F., Lingvay, I., McGowan, B. M., Rosenstock, J., Tran, M. T. D., Wadden, T. A., Wharton, S., Yokote, K., Zeuthen, N., Kushner, R. F., & STEP 1 Study Group. (2021). Once-weekly semaglutide in adults with overweight or obesity. New England Journal of Medicine, 384(11), 989–1002. https://doi.org/10.1056/NEJMoa2032183