Evaluation of Outcomes After Initiating Triple Antidiabetic Therapy with a GLP-1 RA in an Integrated Health Care System

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ABSTRACT

BACKGROUND: Type 2 diabetes (T2D) is characterized by chronic hyperglycemia and can lead to life-threatening complications if not treated. A stepwise and patient-centered approach is recommended when managing patients with T2D. Metformin is the preferred first-line agent, while sulfonylureas (SU) are often chosen as second-line agents. If a patient's hemoglobin A1c (A1c) goal is not achieved despite 3 months of treatment with dual therapy, then triple therapy is recommended. However, due to the lack of head-to-head trials for different triple antidiabetic regimens, the recommendations are unclear for selection of an optimal third-line agent.

OBJECTIVE: To evaluate the comparative effectiveness of a glucagon-like peptide-1 receptor agonist (GLP-1 RA) compared with a thiazolidinedione (TZD) or insulin as a third-line add-on therapy in patients who have not achieved A1c goals while receiving metformin and SU dual therapy in the real-world setting within an integrated health care system.

METHODS: This is a retrospective cohort study of adult patients with T2D who were not at goal A1c while on dual therapy with metformin and an SU and initiated triple antidiabetic therapy. The primary outcome was the proportion of patients who achieved goal A1c within 3-7 months after starting triple therapy with a GLP-1 RA compared with a TZD or insulin. Goal A1c was defined as an A1c of <7% for patients aged less than 65 years and A1c of <8% for patients aged 65 years or older. Secondary outcomes included mean change in A1c, mean change in weight, and the proportion of patients with an emergent health care encounter due to a hypoglycemic event. Propensity score matching was used to select comparison groups from the insulin and TZD groups with similar baseline characteristics to the GLP-1 RA group in a 4:1 ratio.

RESULTS: 274 patients initiated a GLP-1 RA in addition to dual therapy with metformin and an SU. A propensity matched group of 1,096 patients who initiated insulin and 1,096 patients who initiated a TZD were selected as the control groups. Addition of a GLP-1 RA resulted in a significantly lower proportion of patients achieving goal A1c (23.0%) compared with the addition of a TZD (30.8%, $P=0.011$). There was no significant difference with the addition of a GLP-1 RA when compared with insulin (24.1%, $P=0.704$).

CONCLUSIONS: This study reflects data from real-world practice in a large integrated health care system. Significantly less patients achieved goal A1c with the addition of a GLP-1 RA as a third-line add-on option to dual therapy with metformin and an SU compared with the addition of a TZD. Providers and patients should carefully weigh the risks and benefits of different antidiabetic agents when choosing triple therapy regimens.

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What is already known about this subject

- A patient-centered approach should be used when initiating antidiabetic drug regimens per the American Diabetes Association and the American Association of Clinical Endocrinologists/American College of Endocrinology guidelines.
- If goal hemoglobin A1c (A1c) is not achieved after monotherapy with an antidiabetic agent, combination therapy is then indicated.

What this study adds

- Addition of a glucagon-like peptide-1 receptor agonist (GLP-1 RA) as a third-line add-on option resulted in a significantly lower proportion of patients achieving goal A1c compared with the addition of a thiazolidinedione.
- Study results showed there was no difference in the proportion of patients achieving goal A1c with the addition of a GLP-1RA compared with the addition of insulin as a third-line add-on option.

Type 2 diabetes (T2D) is a metabolic disorder characterized by chronic hyperglycemia and is a public health concern in the United States.¹ Failure to achieve glycemic goals significantly increases the risk of complications, including cardiovascular disease and microvascular complications and death. A stepwise and patient-centered approach is recommended when managing patients with T2D.²

There are 12 classes of antidiabetic medications that are approved by the U.S. Food and Drug Administration (FDA) to treat T2D. Metformin is the preferred first-line therapy, unless contraindicated, based on recommendations from the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists/American College of Endocrinology, and results from a large meta-analysis.¹⁻³ Metformin is preferred because of its effectiveness at reducing hemoglobin A1c (A1c; by 1%-2%), safety profile, low cost, and potential to reduce cardiovascular events and death.¹⁻⁴ Patients who have not achieved goal A1c with monotherapy will require additional glucose-lowering therapies to reach goal A1c. Each new class of noninsulin agents added is estimated to lower A1c by approximately 0.9%-1.1%; however, there is no consensus for the selection of optimal second- or third-line add-on therapies.^{2,5}

FIGURE 1 Patient Selection Cohort Flowchart

*Patients could have met more than 1 exclusion criteria.

^bA1c goal was defined as an A1c of <7% for patients aged <65 years and A1c of <8% for patients aged 65 years or older.

A1c = hemoglobin A1c; GLP-1 RA = glucagon-like peptide-1 receptor agonist; TZD = thiazolidinedione.

Antidiabetic drug classes that are commonly chosen as second- or third-line agents include sulfonylureas (SUs), thiazolidinediones (TZDs), insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors, with the latter 3 being the more recent drug classes approved within the past 13 years.^{2,3} Since SUs, TZDs, and insulin are older drug classes, there is extensive experience using these agents. Advantages for all 3 drug classes include their low cost (only regular and NPH in the insulin class) and efficacy at lowering A1c, while weight gain is a disadvantage. A class specific advantage of SUs is the ability to decrease microvascular risk, and a disadvantage is the higher risk of hypoglycemia. Other advantages of TZDs include the low risk of hypoglycemia and the ability of some TZDs to decrease triglycerides and cardiovascular events, while disadvantages include reduction in bone mineral density and potential to cause edema, especially in heart failure patients. Advantages of insulin include the theoretically unlimited efficacy and universal response for all patients, while disadvantages include risk of hypoglycemia, the injectable formulation, and high cost of the newer analog insulin agents.^{2,3}

The FDA approved the first GLP-1 RA in 2005, and there have been multiple approvals since, including exenatide (Byetta/Bydureon), liraglutide (Victoza), albiglutide (Tanzeum), dulaglutide (Trulicity), lixisenatide (Lyxumia), and semaglutide (Ozempic).⁶ GLP-1 RAs may be an appealing option for the treatment of T2D because of their ability to promote weight loss, low hypoglycemia risk, potential to restore beta cell function, availability in once-weekly dosing formulations, and increasing evidence for reduced cardiovascular events.^{2,6,7} However, disadvantages to GLP-1 RAs include high cost, injection formulation, potential gastrointestinal side effects, and risk for pancreatitis.²

Because there are a plethora of antidiabetic agents approved for the treatment of T2D, it is imperative to balance the different characteristics of antidiabetic agents for the management of T2D. The ADA recommends selection of an antidiabetic agent based on patient preference and specific factors, such as efficacy, cost, side effects, effect on weight, comorbidities, prevention of complications, drug formulation, and hypoglycemia risk.² Studies comparing different antidiabetic combinations can help guide clinicians in selecting optimal therapies.

The ongoing Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) study will compare the long-term effectiveness and safety profile of dual therapy with SUs, DPP-4 inhibitors, GLP-1 RAs, and basal insulin when added to metformin monotherapy.⁸ However, studies comparing the effectiveness of different triple therapy combinations are still lacking but could help guide clinicians in selecting optimal therapies. Therefore, the purpose of this study was to evaluate the outcomes of a GLP-1 RA compared with a TZD or insulin as the third add-on agent in patients who have not achieved A1c goal while receiving metformin and SU dual therapy in the real-world setting within an integrated health care system.

Methods

Study Design and Setting

This study was designed as a retrospective cohort study that analyzed data from electronic databases within Kaiser Permanente Southern California (KPSC) and Northern California (KPNC) regions. Kaiser Permanente is an integrated health care delivery organization that cares for over 8 million members in California. Members receive comprehensive medical services such as hospital, ambulatory, pharmacy, laboratory, and ancillary care within the same system, with data continuously updated in an electronic medical record since 1995. This study was approved by the KPSC and KPNC institutional review boards and has received a waiver for informed consent.

Patient Selection

Health plan pharmacy databases were used to identify adult patients with T2D who were treated with metformin and SU dual therapy between January 2006 and June 2016 and initiated a third antidiabetic agent. T2D was defined based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM 250.0x and 250.2x) and the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM E11.x) codes. Patients were excluded if they did not have baseline and follow-up A1c measurements; were not members of KPSC or KPNC for the 6 months before initiation of triple therapy; were at goal A1c at time of initiation of triple therapy; initiated a triple therapy agent other than a TZD, insulin, or GLP-1 RA; or were not treated with the triple therapy regimen for at least 90 days.

Goal A1c was defined as an A1c of <7% for patients aged younger than 65 years and an A1c of <8% for patients aged 65 years or older per the ADA recommendations² and Kaiser Permanente guidelines for uncomplicated T2D patients. The date when the triple therapy agent was initiated was defined as the index date. Baseline A1c was defined as the closest A1c to the index date, within 90 days before the index date. Follow-up A1c was defined as the first A1c measured within 3-7 months after the index date. Patients were followed until the end of

their Kaiser Permanente membership, they discontinued or switched any drugs in the triple therapy regimen, or the study end date of December 31, 2016, whichever occurred first.

The study group included patients on dual therapy with metformin and an SU who started a GLP-1 RA as the triple therapy agent (Figure 1). The 2 control groups were patients on dual therapy with metformin and an SU who started either insulin or a TZD as the triple therapy agent. Controls were matched in a 4:1 ratio for each study group patient based on the propensity score. Propensity score matching was used to minimize selection bias by balancing differences in baseline characteristics and demographics between the treatment groups. The propensity score was estimated using a logistic regression model, in which patients receiving a GLP-1 RA were regressed on various pretreatment characteristics. The pretreatment characteristics used in propensity score matching were age, gender, race, baseline A1c, time on triple therapy, duration of T2D, Charlson Comorbidity Index (CCI) score, hypertension, hyperlipidemia, and metformin at maximum dose. Maximum dose of metformin was defined as a dose ≥ 2 grams per day.

Endpoints

The primary outcome was the proportion of patients that achieved goal A1c within 3-7 months after the index date. The secondary outcomes were mean change in A1c from baseline to follow-up A1c, mean change in weight from baseline until patient completed the triple therapy regimen, and the proportion of patients with an emergency department visit or hospitalization due to a hypoglycemic event while the patient was on the triple therapy regimen. Hypoglycemia was defined based on the ICD-9-CM codes 251.x and the ICD-10-CM codes E16.x, E09.64x, E11.64x, and E13.64x.

Statistical Analysis

Approximately 222 patients were required in the study group and 888 patients in each control group to achieve an absolute 10% improvement in reaching goal A1c in the control group, assuming 25% of patients in the GLP-1 RA group would reach goal A1c, for an 80% power on the significance level of 0.05. Descriptive analyses were performed to compare all the baseline characteristics and demographics before and after propensity score matching for the study group and controls. Pearson's chi-square test was used to compare categorical variables, and Student's t-test was used to compare continuous variables. The primary endpoint was analyzed using logistic regression, adjusting for potential confounders. Two multivariate logistic regression models were fitted to estimate the odds ratio (OR) for achieving A1c goal with 95% confidence intervals (CI) for patients in the GLP-1 RA group compared with those in the insulin and TZD groups, respectively. Additional covariables in the logistic regression included age, gender, baseline A1c, race, CCI score, hypertension, hyperlipidemia, and metformin

TABLE 1 Baseline Demographics and Characteristics by Treatment Group Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
	Insulin n = 37,831	TZD n = 20,207	GLP-1 RA n = 274	Insulin n = 1,096	TZD n = 1,096	GLP-1 RA n = 274
Age, mean $\pm$ SD	57.4 $\pm$ 10.8 <i>P</i> < 0.001	56.8 $\pm$ 10.0 <i>P</i> < 0.001	54.0 $\pm$ 8.8	54.0 $\pm$ 11.1 <i>P</i> = 0.973	54.4 $\pm$ 10.5 <i>P</i> = 0.542	54.0 $\pm$ 8.8
Male, % (n)	51.8 (19,608) <i>P</i> = 0.040	55.3 (11,169) <i>P</i> = 0.001	45.6 (125)	49.4 (541) <i>P</i> = 0.268	45.4 (498) <i>P</i> = 0.957	45.6 (125)
White, % (n)	37.6 (14,219) <i>P</i> < 0.001	33.3 (6,737) <i>P</i> < 0.001	49.3 (135)	48.5 (531) <i>P</i> = 0.994	50.9 (558) <i>P</i> = 0.953	49.3 (135)
Baseline A1c, mean $\pm$ SD	9.6 $\pm$ 1.6% <i>P</i> < 0.001	8.9 $\pm$ 1.3% <i>P</i> = 0.0134	9.1 $\pm$ 1.3%	9.1 $\pm$ 1.4% <i>P</i> = 0.895	9.0 $\pm$ 1.5% <i>P</i> = 0.292	9.1 $\pm$ 1.3%
CCI, median, IQR	3, 2-4 <i>P</i> = 0.220	2, 1-4 <i>P</i> < 0.001	3, 2-4	3, 2-4 <i>P</i> = 0.840	3, 1-4 <i>P</i> = 0.935	3, 2-4
HTN, % (n)	71.7 (27,121) <i>P</i> = 0.380	75.0 (15,145) <i>P</i> = 0.744	74.1 (203)	72.5 (795) <i>P</i> = 0.606	75.2 (824) <i>P</i> = 0.708	74.1 (203)
HLD, % (n)	70.9 (26,811) <i>P</i> = 0.139	63.9 (12,920) <i>P</i> = 0.329	66.8 (183)	68.3 (748) <i>P</i> = 0.643	66.8 (732) <i>P</i> = 1.000	66.8 (183)
Metformin at maximum dose, % (n)	52.8 (19,984) <i>P</i> = 0.319	56.6 (11,446) <i>P</i> = 0.790	55.8 (153)	49.5 (543) <i>P</i> = 0.062	53.5 (586) <i>P</i> = 0.481	55.8 (153)

Note: *P* values represent comparisons with the GLP-1 RA group.

CCI=Charlson Comorbidity Index; GLP-1 RA=glucagon-like peptide-1 receptor agonist; HTN=hypertension; HLD=hyperlipidemia; IQR=interquartile range; SD=standard deviation; TZD=thiazolidinedione.

at maximum dose. *P* values < 0.05 were considered statistically significant. The SAS statistical package, version 9.4, was used for all analysis (SAS Institute, Cary, NC).

Results

Patients

During the study period (January 2006-June 2016), a total of 225,816 members were identified as having started a triple therapy antidiabetic regimen. A total of 167,504 patients were excluded due to not having baseline and follow-up A1c measurements (21%); not being a Kaiser Permanente member for ≥ 6 months before initiation of triple therapy (15%); were already at goal A1c (15%); initiated triple therapy with agents other than insulin, TZD, or GLP-1 RA (18%); or did not continue their triple therapy regimen for at least 90 days (10%). Patients could have been excluded due to more than 1 criteria. The remaining 58,312 patients met the inclusion criteria, with 37,831 patients in the insulin treatment group, 20,207 in the TZD treatment group, and 274 patients in the GLP-1 RA treatment group (Figure 1).

Before propensity score matching, there were many significant differences in baseline characteristics between the treatment groups. For propensity score matching, each patient who started a GLP-1 RA was matched to 4 patients who started insulin and 4 patients who started a TZD, which resulted in 1,096 patients in each control group. The mean age of all patients was 54.1 (SD $\pm$ 10.6) years old, and the average baseline A1c was 9.1 (SD $\pm$ 1.4). Forty-seven percent of patients were male; 50% were white; 74% had hypertension; 67% had hyperlipidemia;

and 52% were using metformin at the maximum dose. When comparing the 2 matched groups with the study group, there were no significant differences in baseline demographics and baseline A1c (Table 1).

Blood Glucose Control

Significantly more patients in the TZD group than in the GLP-1 RA group met the primary endpoint of achieving goal A1c within 3 to 7 months of the index date (30.8% vs. 23.0%, *P* = 0.011). There was no difference in achieving goal A1c between the insulin and GLP-1 RA treatment arms (24.1% vs. 23.0%, *P* = 0.704; Table 2). There was also no difference in the mean change in A1c when comparing the GLP-1 RA treatment group (-0.91 [SD $\pm$ 1.35]%) with insulin (-0.97 [SD $\pm$ 1.48]%, *P* = 0.530) or TZD (-1.04 [SD $\pm$ 1.51]%, *P* = 0.162; Table 2).

In the multivariate logistic regression model comparing GLP-1 RA with TZD (Table 3) after adjustment for age, baseline A1c, and other prespecified variables, patients in the GLP-1 RA group were 29% (*P* = 0.041) less likely to achieve A1c goal compared with patients in the TZD group (Table 3). The most significant positive predictors of achieving A1c goal were older age (OR = 1.04; 95% CI = 1.03-1.06) and having hypertension (OR = 1.51; 95% CI = 1.09-2.09). Significant negative predictors of achieving A1c goal were a higher baseline A1c (OR = 0.61; 95% CI = 0.54-0.69) and being black (OR = 0.64; 95% CI = 0.42-0.98) or Hispanic (OR = 0.65; 95% CI = 0.48-0.88) versus white.

TABLE 2 Effect of Adding a Triple Therapy Agent on A1c, Weight, and Hypoglycemic Events

	Insulin n = 1,096	TZD n = 1,096	GLP-1 RA n = 274
Patients achieving goal A1c, % (n)	24.1 (264) P = 0.704	30.8 (338) P = 0.011	23.0 (63)
Change in A1c, mean ± SD	-0.97 ± 1.48% P = 0.530	-1.04 ± 1.51% P = 0.162	-0.91 ± 1.35%
Hypoglycemic event, % (n)	0.18 (2) P = 0.479	0.27 (3) P = 0.386	0 (0)
Patients with pre- and postweight measured, n	336	247	117
Baseline weight in kg, mean ± SD	98.1 ± 26.3 P = 0.078	96.7 ± 25.0 P = 0.024	103.0 ± 25.4
Change in weight in kg, mean ± SD	0.6 ± 3.8 P = 0.134	1.9 ± 4.0 P = 0.003	-0.6 ± 8.1

Note: P values represent comparisons with the GLP-1 RA group.

A1c = hemoglobin A1c; GLP-1 RA = glucagon-like peptide-1 receptor agonist; kg = kilogram; SD = standard deviation; TZD = thiazolidinedione.

In the multivariate logistic regression model comparing GLP-1 RA with insulin (Table 4), there was no difference in the likelihood to achieve A1c goal if patients were in the GLP-1 RA or insulin groups. The most significant positive predictor of achieving A1c goal was older age (OR = 1.05; 95% CI = 1.04-1.07). The most significant negative predictors of achieving A1c goal were a higher baseline A1c (OR = 0.64; 95% CI = 0.57-0.72) and being Hispanic (OR = 0.60; 95% CI = 0.43-0.84) versus white.

Body Weight

Baseline weight and follow-up weight were only available in some patients. The mean baseline weight for the GLP-1 RA group was the highest (103.0 [SD ± 25.4] kg, n = 117) and was significantly different compared with the TZD group (96.7 [SD ± 25.0] kg, n = 247, $P = 0.024$) but not significantly different compared with the insulin group (98.1 [SD ± 26.3] kg, n = 336, $P = 0.078$). Compared with a weight loss of -0.6 (SD ± 8.1) kg in the GLP-1 RA group, addition of a TZD resulted in a mean weight gain of 1.9 (SD ± 4.0) kg, which was significantly different ($P = 0.003$; Table 2). The addition of insulin resulted in a mean weight gain of 0.6 (SD ± 3.8) kg, which was not significantly different ($P = 0.134$) from the GLP-1 RA group.

Hospital Encounters Due to Hypoglycemic Event

There were no incidences of hypoglycemic events resulting in hospitalization in any of the treatment arms during the study period. Two emergency department visits due to a hypoglycemic event occurred in the insulin group (0.18%); 3 events occurred in the TZD group (0.27%); and none occurred in the GLP-1 RA group. However, these were not statistically different among the groups.

Discussion

In this retrospective cohort study, we evaluated the effects of adding a GLP-1 RA compared with insulin or TZD in patients

with T2D who were not at goal A1c while on metformin and SU dual therapy. The proportion of patients who met the primary endpoint of achieving goal A1c within 3-7 months of the index date was significantly lower in the GLP-1 RA group than in the TZD group. Although our follow-up time was shorter, our findings are similar to a previous study comparing albiglutide, a GLP-1 RA, versus pioglitazone, a TZD, when added to metformin and glimepiride, an SU, dual therapy.⁹ Home et al. (2015) found that at week 52, more participants using pioglitazone achieved A1c goals of <7.0% and <7.5% ($P = 0.048$ and $P = 0.007$, respectively) compared with albiglutide and had a significantly larger mean (± standard error [SE]) decrease in A1c (0.80 [SE ± 0.06]%) compared with use of albiglutide (0.55 [SE ± 0.06]%, $P = 0.001$).⁹ In comparison, our study did not find any statistical differences in the reduction of A1c levels in any of the treatment arms. Differences in study design (real world vs. randomized, parallel group) and follow-up time (3-7 months vs. 52 weeks) may account for the variances in results. However, the lack of statistical difference in reduction of A1c levels was consistent with 2 meta-analyses that evaluated reduction in A1c for different triple therapy combinations.^{10,11} The meta-analyses reported that different triple therapy combinations were similar in their ability to control diabetes and the differences were between the adverse effects.¹¹

In terms of body weight, we found a favorable change in body weight with GLP-1 RAs compared with TZDs, which was also reported in previous studies and meta-analyses.⁹⁻¹¹ The mean (± SE) weight change found by Home et al. was -0.42 (± 0.2) kg with albiglutide and +4.4 (± 0.2) kg ($P < 0.001$) with pioglitazone.⁹ The adjusted mean change in weight was smaller in our study, since we had a shorter follow-up time than Home et al., and our sample size was significantly smaller. When comparing effect on weight for GLP-1 RAs versus insulin, insulins are commonly associated with weight gain and GLP-1 RAs with weight loss.^{2,11} However, our study found no difference in

TABLE 3 Multivariate Logistic Regression of Achieving Goal A1c When Comparing GLP-1 RA with TZD as the Third-Line Triple Therapy Agent

Parameter	OR (95% CI)	P Value
Treatment with GLP-1 RA vs. TZD	0.71 (0.51-0.99)	0.041 ^a
Age	1.04 (1.03-1.06)	<0.001 ^a
Female vs. male	1.19 (0.92-1.53)	0.186
Black vs. white	0.64 (0.42-0.98)	0.041 ^a
Hispanic vs. white	0.65 (0.48-0.88)	0.006 ^a
Other vs. white	0.50 (0.31-0.80)	0.004 ^a
Baseline A1c	0.61 (0.54-0.69)	<0.001 ^a
CCI score 1-2 vs. 5+	0.83 (0.59-1.15)	0.263
CCI score 3-4 vs. 5+	0.66 (0.47-0.93)	0.017 ^a
Hypertension	1.51 (1.09-2.09)	0.012 ^a
Hyperlipidemia	0.96 (0.73-1.26)	0.750
Metformin at maximum dose	1.02 (0.79-1.31)	0.881

Note: Both age and baseline A1c are continuous variables; therefore, the OR represents the incremental rate for each unit of increase.

^aStatistically significant at the 0.05 level.

A1c = hemoglobin A1c; CCI = Charlson Comorbidity Index; CI = confidence interval; GLP-1 RA = glucagon-like peptide-1 receptor agonist; OR = odds ratio; TZD = thiazolidinedione.

TABLE 4 Multivariate Logistic Regression of Achieving Goal A1c When Comparing GLP-1 RA to Insulin as the Third-Line Triple Therapy Agent

Parameter	OR (95% CI)	P Value
Treatment with GLP-1 RA vs. insulin	0.98 (0.70-1.36)	0.893
Age	1.05 (1.04-1.07)	<0.001 ^a
Female vs. male	1.01 (0.77-1.32)	0.949
Black vs. white	1.02 (0.68-1.53)	0.941
Hispanic vs. white	0.60 (0.43-0.84)	0.003 ^a
Other vs. white	0.53 (0.31-0.90)	0.019 ^a
Baseline A1c	0.64 (0.57-0.72)	<0.001 ^a
CCI score 1-2 vs. 5+	0.89 (0.63-1.25)	0.491
CCI score 3-4 vs. 5+	0.92 (0.64-1.32)	0.648
Hypertension	0.94 (0.67-1.30)	0.702
Hyperlipidemia	1.17 (0.86-1.58)	0.313
Metformin at maximum dose	0.98 (0.75-1.28)	0.875

Note: Both age and baseline A1c are continuous variables; therefore, the OR represents the incremental rate for each unit of increase.

^aStatistically significant at the 0.05 level.

A1c = hemoglobin A1c; CCI = Charlson Comorbidity Index; CI = confidence interval; GLP-1 RA = glucagon-like peptide-1 receptor agonist; OR = odds ratio.

body weight change between the insulin and GLP-1 RA groups. Our results may reflect having SUs as part of the triple therapy regimen, since SUs are associated with weight gain.

Although insulin is usually associated with more severe hypoglycemic events while GLP-1 RAs and TZDs are not commonly associated with hypoglycemic events,^{2,11} we reported no difference in hospital encounters due to a hypoglycemic event in any of the treatment groups. Because the incidence of patients with a hospital encounter due to a hypoglycemic event was very low in all treatment groups, this study was too small to detect a clinically significant rate of hypoglycemia for any of the triple therapy combinations.

According to the ADA, GLP-1 RAs and TZDs have high efficacy in terms of A1c reduction, with insulin having the highest efficacy.¹² Although there may be many benefits to the newer antidiabetic agents, newer drugs are also often associated with higher costs compared with older therapies. As interest increases from patients or providers to trial newer antidiabetic agents, head-to-head trials comparing the outcomes of different triple antidiabetic regimens will be vital to help in optimal medication selection.

Because the literature is currently limited, the rationale for our study was to provide real-world outcomes comparing the effectiveness of different triple antidiabetic regimens. Our findings demonstrate that although GLP-1 RAs may offer the benefit of weight loss compared with use of TZDs, a smaller proportion of patients achieved A1c goal. Also, in our patient population, patients who were of older age were more likely to reach goal A1c, while patients with a higher baseline A1c or were Hispanic were less likely to reach goal A1c.

While this study provides clinicians with more information regarding the outcomes of different triple therapy regimens to help them determine optimal antidiabetic drug therapy for patients, these results should be combined with other available literature to assist in selecting optimal drug therapy. Achieving goal A1c is multifactorial as clinicians must consider patient characteristics and comorbid conditions in addition to medication efficacy and other medication-specific factors when selecting drug regimens.

There were many strengths to this study. Since this is a real-world study, the results reflect how patients are managed in a large integrated health care setting, accounting for real-world practice and variations in medication adherence and diet and lifestyle factors. Furthermore, because Kaiser Permanente is an integrated health care system, it is in a unique position to be able to collect comprehensive data, such as patient outcomes, laboratory results, and prescription information for all patients. Finally, propensity score matching was used to minimize confounding variables and selection bias that may affect the treatment outcomes.

Limitations

Limitations to this study include the small sample size for the study group and short follow-up time. Due to the retrospective nature of this study, there was the potential for selection bias from confounding variables that influence why patients are selected for particular treatment strategies. Our health care system allows providers to prescribe any antidiabetic therapy they feel are beneficial to the member. Therefore, observable variables were used to find controls that matched the GLP-1

RA patients using propensity score matching. Patients may also have had different A1c goals than what was defined in this study due to their unique risk factors.

Another limitation is that this study did not account for the specific injectable or oral product used within each drug class, if doses were appropriately titrated or not, or if patients were adherent to their medications. This limitation may have had the most effect on the insulin control group, since dosing for insulin is not as straight forward as other antidiabetic agents. Besides hospital encounters due to hypoglycemic events, this study did not assess the safety profile of the different triple therapy regimens.

Finally, the results may not be generalizable, since Kaiser Permanente has programs to assist in diabetes management, whereas other health care systems may or may not have similar resources to manage their patients with diabetes.

Conclusions

This study explored the comparative effectiveness of a GLP-1 RA compared with insulin or a TZD added on to dual therapy with metformin and an SU. We found that the addition of a GLP-1 RA as the third-line add-on option resulted in significantly less patients who achieved goal A1c compared with the addition of a TZD; patients in the GLP-1 RA group experienced weight loss compared with weight gain in patients in the TZD group; and there was no difference in A1c or weight outcomes when comparing the GLP-1 RA group to the insulin group. This study provides data on real-world outcomes for different triple therapy regimens that clinicians can consider when selecting triple therapy regimens. To provide further information, future studies should focus on a larger sample size, as well as other newer antidiabetic agents; should account for an insulin titration regimen; or should include additional outcomes such as effect on cardiovascular outcomes.

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DISCLOSURES

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