INTRODUCTION

Type 2 diabetes (T2D) is a metabolic disorder that affects the body’s ability to produce or use insulin efficiently, leading to chronic hyperglycemia and long-term microvascular and macrovascular complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. Several studies suggest that lowering hemoglobin A1C (HbA1C) to 7% can reduce these long-term complications.1

Metformin has long been recommended as a first-line treatment for the management of T2D in adults unless contraindications or adverse effects preclude its use, but add-on glucose-lowering drugs may be required to help patients meet their glycemic goals.2,3 Sulfonylureas were commonly prescribed as add-ons to metformin because they are available as inexpensive generics and can lower HbA1C by 1% to 2%.4 A study by Cook et al5 concluded that glycemic control is improved after the addition of sulfonylureas to metformin. However, a worsening of glycemic control is seen as early as 6 months for some patients, which suggests that insulin therapy or the addition of a third agent is necessary.5 Clinical studies have evaluated the safety and efficacy of triple-combination antidiabetic therapy, showing that triple therapy is superior or comparable to dual therapy.6-8

There are limited studies that evaluate the newer glucose-lowering agents as a third-line add-on agent after metformin and a sulfonylurea. A retrospective study by Levin et al9 evaluated outcomes for 51,771 adult patients with T2D previously treated with 2 oral antidiabetic agents and then treated with a third antidiabetic agent (any oral diabetic agent versus a glucagon-like peptide-1 receptor agonist [GLP1RA] versus insulin). The potential oral agents included metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitors (DPP4is), thiazolidinedione (TZD), meglitinide, or α-glucosidase inhibitors. After a 2-year follow-up, the change in HbA1C from baseline was −0.88% for the insulin group, −0.33% for the GLP1RA group, and −0.64% for the oral diabetic agent group. However, the authors did not make clear recommendations for third add-on agents to metformin plus a sulfonylurea. This study compared the effectiveness and safety of dipeptidyl peptidase-4 inhibitors (DPP4is) to thiazolidinedione (TZD) or insulin as a third add-on agent to metformin plus a sulfonylurea in an integrated health care setting.

**ORIGINAL RESEARCH ARTICLE**

**EVALUATION OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS VERSUS THIAZOLIDINEDIONES OR INSULIN IN PATIENTS WITH TYPE 2 DIABETES UNCONTROLLED WITH METFORMIN AND A SUFYONYLUREA IN A REAL-WORLD SETTING**

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**ABSTRACT**

Background: Guidelines do not make clear recommendations for third add-on agents to metformin plus a sulfonylurea. This study compared the effectiveness and safety of dipeptidyl peptidase-4 inhibitors (DPP4is) to thiazolidinedione (TZD) or insulin as a third add-on agent to metformin plus a sulfonylurea in an integrated health care setting.

Methods: This retrospective database cohort study included adults with type 2 diabetes not at goal hemoglobin A1C (HbA1C) who initiated DPP4i, TZD, or insulin as a third add-on agent to metformin plus a sulfonylurea from January 2006 to June 2016. Primary outcomes were the proportion of patients who achieved goal HbA1C after starting the third add-on agent and change in HbA1C. Subgroup analysis was performed for patients with baseline HbA1C greater than 9%.

Results: In this study, 2080 patients started on a DPP4i were matched to 8320 patients started on TZD and to 8320 patients taking insulin. A significantly higher percentage of patients taking TZD reached goal HbA1C (31.0% versus 23.6%; p < 0.05) and had a significantly larger HbA1C reduction (−0.94% ± 1.34% versus −0.79% ± 1.23%; p < 0.01) compared to patients taking a DPP4i. No difference in the percentage of patients meeting goal HbA1C nor change in HbA1C was demonstrated between insulin versus DPP4i regimens. For patients with baseline HbA1C greater than 9%, insulin or TZD resulted in a significantly higher proportion of patients achieving goal HbA1C compared to DPP4i (17.3% and 19.0% versus 12.4%, respectively; p < 0.01).

Conclusion: TZD was more effective as DPP4i but DPP4i was as effective as insulin as a third add-on agent in the overall study population. Insulin was more effective than DPP4i only in the subgroup analysis of patients with baseline HbA1C greater than 9%.

Keywords: diabetes, DPP-4 inhibitors, insulin, metformin, outcomes, real-world, sulfonylurea, thiazolidinediones
not compare the outcomes among these groups for statistical significance. In addition, there was no evaluation performed for specific oral antidiabetic agents.

Two network meta-analyses have evaluated the effect of adding a third antidiabetic agent for adult patients with T2D who did not achieve glycemic control with metformin and a sulfonylurea.\(^{10,11}\) Using data from 9 trials, Gross et al\(^{10}\) concluded that there were notably higher HbA\(_{1C}\) reductions for patients receiving acarbose, TZD, GLP1RA, DPP4i, or insulin when added as a third agent to metformin and a sulfonylurea compared to placebo. McIntosh et al\(^{11}\) evaluated 33 randomized controlled trials with a minimum 4-week duration. This analysis, which included more active comparison trials, found that insulin, DPP4i, GLP1RA, and TZD led to significant reductions in HbA\(_{1C}\) in combination with metformin and a sulfonylurea, whereas meglitinides and α-glucosidase inhibitors did not.\(^{11}\) Since these meta-analyses used studies that compared active drugs to placebo, the investigators relied on many indirect comparisons and extrapolation of data. There is limited evidence to help clinicians determine a preferred third-line agent.

In an open-label study by Hsia et al,\(^{12}\) 108 patients who had uncontrolled T2D and were taking metformin and a sulfonylurea were treated with add-on sitagliptin, a DPP4i, and compared to a historical control of similar patients treated with an add-on TZD. Patients in the TZD group achieved a larger mean HbA\(_{1C}\) reduction compared to that of patients in the sitagliptin group (\(-2.0\%\) versus \(-1.3\%\); \(p = 0.006\)). In a similar open-label study by Liu et al,\(^{13}\) the mean change in HbA\(_{1C}\) from baseline was \(-0.94\% \pm 0.12\%\) for 59 patients treated with pioglitazone and \(-0.71\% \pm 0.12\%\) for 60 patients treated with sitagliptin, but these results were not statistically significant due to the small sample size (\(p = 0.16\)). Mean weight gain was significantly higher in the pioglitazone group (\(p < 0.01\)).

At the time this study was conducted, guidelines available to aid clinicians in the decision-making process for selecting the third agent were lacking. Prior to 2018, both the American Diabetes Association (ADA)\(^3\) Standards of Medical Care in Diabetes as well as the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)\(^3\) Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan did not provide recommendations for when to use a specific drug or class of drugs as a second or third add-on agent to metformin due to the lack of comparative efficacy. Instead, they recommended a stepwise approach to managing treatment for patients with T2D, emphasizing a patient-centered approach to care by considering patient preferences, needs, and values.\(^{2,3}\)

The guidelines suggested that if patients did not attain glycemic control after 3 months of metformin monotherapy, then the addition of another glucose-lowering drug is recommended. The appropriate drug to add on could be selected after consideration of several factors, including the HbA\(_{1C}\) reduction needed to reach goal, risk of hypoglycemia, effects on weight, adverse effect profile, and cost.\(^3\)

The National Committee for Quality Assurance developed a standardized performance Healthcare Effectiveness Data and Information Set for managed care organizations. Under the comprehensive diabetes care measure, poor HbA\(_{1C}\) control has been listed as one of the quality indicators since 2000.\(^7,8\) In efforts to improve the quality of diabetes care and achieve Healthcare Effectiveness Data and Information Set measures, there has been a growing interest in the role of newer antidiabetic agents, such as DPP4is, as a third-line add-on agent after metformin and a sulfonylurea. However, these agents may have varying levels of HbA\(_{1C}\) reduction, unclear long-term safety, and high costs compared to traditional third-line add-on agents such as insulin and TZD.

Studies evaluating triple-therapy combinations are limited and are needed to help clinicians determine optimal therapeutic options. This study evaluates the comparative effectiveness and safety of DPP4i versus TZD or insulin as a third-line add-on option to metformin and a sulfonylurea in an integrated health care system.

**METHODS**

**Data Source**

This retrospective cohort study was conducted within the Kaiser Permanente Northern and Southern California Regions, which are large not-for-profit integrated health care systems covering more than 8 million patients. A comprehensive electronic medical record system captured all interactions and aspects of care within the health care delivery system since 2006. This included demographics, membership and benefits, inpatient and outpatient encounters, laboratory test results, and prescription records. Institutional review boards in the Kaiser Permanente Northern and Southern California Regions reviewed and approved this study. Informed consent was waived due to the retrospective nature of the study.

**Patient Selection**

This study included all patients who were not at goal HbA\(_{1C}\) after receiving dual therapy with metformin and a sulfonylurea for at least 90 days and initiated triple therapy with DPP4i, insulin, or TZD during January 2006 to June 2016. The date of initiation was defined as the index date. The definition of goal HbA\(_{1C}\) depended on each patient’s age. Goal HbA\(_{1C}\) was defined as less than 7% for patients younger than 65 years or less than 8% for patients age
65 years or older. Patients must have had a diagnosis of T2D, which was defined as having at least one International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification diagnosis code (ICD-9-CM 250.0x and 250.2x or ICD-10-CM E11.x, respectively) within 12 months prior to the index date. Only patients aged 18 years or older on the index date were included. In addition, patients must have had continuous medical and pharmacy benefits for at least 6 months before initiation of triple therapy, a baseline HbA1c measured within 6 months prior to the index date, and a follow-up HbA1c measured within 3 to 7 months after the index date. Dose changes were allowed during the follow-up period. Patients must have had evidence of picking up prescriptions for all 3 agents for at least the first 90 days from the index date. Patients were followed until the end of membership, the end of their triple-therapy regimen, death, or the study end date of December 31, 2016, whichever occurred first.

The study group was defined as patients taking metformin and a sulfonylurea who started on DPP4i as a third-line add-on agent (+DPP4i), whereas the 2 control groups included patients taking metformin and a sulfonylurea who started on TZD or insulin as a third-line add-on agent (+TZD or +insulin, respectively).

To minimize the differences in baseline demographics, each study group patient was matched to 4 patients from each control group using propensity score matching without replacement to adjust for treatment selection bias. The conditional probability propensity score of receiving DPP4i was estimated using logistic regression with the following covariates: demographics (age, sex, race), baseline HbA1c, duration of T2D, a diagnosis of hypertension or hyperlipidemia, metformin at maximum dose (2 g/d), and health status defined by the Charlson comorbidity index (CCI). The matched patients in the control groups were selected by using the nearest neighbor matching method.

Study Outcomes

The primary outcomes were the proportion of patients who achieved goal HbA1c within 3 to 7 months and change in HbA1c. Secondary outcomes included mean change in body weight and proportion of patients with a hospital encounter or emergency department (ED) visit due to a hypoglycemic event. Follow-up HbA1c results were measured within 3 to 7 months after the index date. If patients had multiple HbA1c measurements within the allotted time frame, then the latest HbA1c was used. Hypoglycemia was defined as an ED visit or hospitalization encounter with a primary diagnosis of ICD-9-CM (251.X) or ICD-10-CM (E16.X, E09.64X, E11.64X, E13.64X) codes during the time when patients were receiving the triple-therapy regimen.

In addition, a subgroup analysis was performed on the primary outcome for patients with an HbA1c greater than 9% at baseline. This analysis was performed due to interest regarding how these third-line add-on therapies performed for this subset of patients with uncontrolled T2D.

Statistical Analysis

Assuming that 20% of patients would attain goal HbA1c, 695 patients were needed in the study group and 2780 matched patients at a ratio of 1:4 were needed in the control group based on an α of 0.05 and 80% power in order to detect an absolute 5% difference in the proportion of patients who met this goal. Descriptive statistics were used to evaluate differences in baseline patient demographics and clinical characteristics between the cohorts before and after propensity score matching. Student t-tests were used to analyze continuous variables, chi-squared tests were used to analyze categorical variables, and Kruskal-Wallis tests were used for nonparametric ordinal variables. A logistic regression was performed to calculate the odds ratio (OR) of achieving goal HbA1c. This regression was controlled for age (as a continuous variable), sex, baseline HbA1c greater than 9%, race, CCI, metformin at maximum dose, and a history of hyperlipidemia or hypertension. Maximum dose for metformin was defined as a dose of 2 g/d or greater. All data were analyzed using SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 225,816 members were identified as starting a triple-therapy glucose-lowering regimen during the study period from January 2006 to June 2016. A total of 167,504 patients were excluded for the following reasons: not being a Kaiser Permanente member for 6 months or longer prior to the initiation of triple therapy (15%); were at goal HbA1c (15%) at baseline; initiated triple therapy with agents other than insulin, TZD, or DPP4i (17%) or did not continue their triple-therapy regimen for at least 90 days (20%); or missing baseline or follow-up HbA1c measurements (22%). Some patients were excluded because they met more than 1 criterion. The remaining 60,118 patients met all of the inclusion criteria, with 37,831 patients in the +insulin treatment group, 20,207 in the +TZD treatment group, and 2080 patients in the +DPP4i treatment group (Figure 1).

There were significant differences in baseline demographic and clinical characteristics among the 2 cohorts before propensity score matching. Patients in the +insulin group had a higher baseline HbA1c compared with the +DPP4i or +TZD groups. In addition, patients in the +insulin group had a higher CCI score, and there were
more patients taking metformin at maximum dose in the +TZD group (Table 1).

After propensity score matching, the cohorts were well matched in all observed baseline variables. There were 2080 patients in the +DPP4i group, which was matched to 8320 patients in the +insulin group and 8320 patients in the +TZD group. For the overall population, the mean age was 58.0 ± 9.9 years, 42.8% of patients were women, 33.8% of patients reported as white, and the mean baseline HbA1C was 8.9% ± 1.3% (Table 1).

Patients reporting Hispanic ethnicity were not significantly different among the study groups (33.0%, 34.3%, and 33.2% for the +insulin, +TZD, and +DPP4i groups, respectively; p = 0.55).

**Proportion at Goal**

The results for the proportion of patients who attained goal are presented in Table 2. When comparing the +DPP4i group to the +insulin group, there was no difference in the percentage of patients who achieved goal HbA1C (24.2% versus 23.6%, respectively; p = 0.58). However, +TZD use resulted in a significantly higher percentage of patients who achieved goal HbA1C compared to +DPP4i use (31.0% versus 23.6%, respectively; p < 0.01).
Change in HbA1C

The mean change in HbA1C is shown in Table 2. When comparing the +DPP4i group to the +insulin group, there was no significant difference in the reduction of HbA1C (-0.79% ± 1.23% versus -0.79% ± 1.31%, respectively; p = 0.97) between the 2 groups. However, the +TZD group had a significantly larger mean HbA1C reduction compared to the +DPP4i group (-0.94% ± 1.34% versus -0.79% ± 1.31%, respectively; p < 0.01).

Hypoglycemia

There was no significant difference in the rate of hospital or ED hypoglycemic events when evaluating the +insulin group (0.41%; p = 0.07) and +TZD group (0.31%; p = 0.19) compared to the +DPP4i group (0.14%) (Table 2).

Weight

In terms of weight, the +insulin and +TZD groups had a significantly larger mean change in weight compared to the DPP4i group, which had a decrease in weight (0.49 ± 4.05 kg and 1.22 ± 3.59 kg versus -0.15 ± 3.33 kg, respectively; p < 0.01) (Table 2).

Patient Population HbA1C Greater than 9%

Results of the subgroup analysis for the patient population with HbA1C greater than 9% at baseline (n = 6597; mean HbA1C = 10.2% ± 1.1%) are summarized in Table 2. The +insulin group had a higher proportion of patients who achieved goal HbA1C compared to the +DPP4i group (17.3% versus 12.4%, respectively; p < 0.01). Similarly, the +TZD group also had a higher proportion of patients who achieved goal HbA1C compared to the +DPP4i group (19.0% versus 12.4%, respectively; p < 0.01) and had a larger mean HbA1C reduction compared to the addition of +DPP4i (-1.71 versus -1.45, respectively; p < 0.01).

Factors Affecting the Odds of Achieving HbA1C Goal

A logistic regression was performed to predict the odds of achieving goal HbA1C among the +DPP4i and +TZD groups. The use of +DPP4i was less likely to help patients attain goal HbA1C (OR = 0.63; 95% CI = 0.56-0.71; p < 0.01) compared to +TZD (Table 3).

There were no statistically significant differences in the odds of achieving goal HbA1C when evaluating +DPP4i compared to insulin (OR = 0.98; 95% CI = 0.87-1.10; p = 0.68) using logistic regression (Table 4).

Patients with a baseline HbA1C greater than 9% were less likely to achieve goal HbA1C when evaluating +DPP4i.
compared to +TZD (OR = 0.67; 95% CI = 0.52-0.86; p < 0.01; Table 3) and +DPP4i compared to insulin (OR = 0.55; 95% CI = 0.42-0.71; p < 0.01; Table 4).

DISCUSSION
In this real-world study, we assessed the comparative effectiveness and safety of third-line add-on options to metformin and sulfonylurea therapy for patients treated from January 2006 to June 2016. Our study demonstrated that there was no difference in the percentage of patients who achieved their goal HbA1C or in the mean HbA1C reduction between the +DPP4i and +insulin groups. However, for patients with a baseline HbA1C greater than 9%, the addition of insulin had a substantially larger mean HbA1C reduction compared to the addition of DPP4i. Theoretically, the absolute decrease in HbA1C is larger with higher baseline HbA1C values and smaller for lower HbA1C values. When appropriately adjusted, insulin has no limit on HbA1C reduction and may be beneficial for patients with a higher baseline HbA1C.

In regard to the comparison of DPP4i to TZD, our findings are similar to that of controlled trials. In an open-label study by Hsia et al,12 patients in the TZD group achieved a larger mean HbA1C reduction compared to that of the sitagliptin group (−2.0% versus −1.3%; p = 0.006). Our study adds to the literature because it draws from an ethnically diverse cohort.

A notably higher percentage of patients achieved their goal HbA1C and a larger mean HbA1C reduction was achieved in the +TZD group versus the +DPP4i group. A potential reason for this difference is that patients with insulin resistance may benefit more from an insulin sensitizer than a drug that acts as a secretagogue. In our study, the majority of TZD prescriptions were prescribed during the first year of the study period (2006). After 2006, TZDs

Table 2. Unadjusted primary and secondary outcomes by study groupsa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DPP4i</th>
<th>Insulin</th>
<th>TZD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>2080</td>
<td>8320</td>
<td>8320</td>
</tr>
<tr>
<td>Proportion achieving HbA1C goal</td>
<td>23.6</td>
<td>24.2</td>
<td>0.58</td>
</tr>
<tr>
<td>Change in HbA1C (mg/dL)</td>
<td>−0.79 ± 1.23</td>
<td>−0.79 ± 1.31</td>
<td>0.97</td>
</tr>
<tr>
<td>Frequency of hypoglycemia, n (%)</td>
<td>3 (0.14)</td>
<td>34 (0.41)</td>
<td>0.07</td>
</tr>
<tr>
<td>Patients, n</td>
<td>758</td>
<td>2351</td>
<td>1829</td>
</tr>
<tr>
<td>Mean change in weight (kg)</td>
<td>−0.15 ± 3.33</td>
<td>0.49 ± 4.05</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Proportion achieving HbA1C goal: baseline HbA1C &gt; 9%</td>
<td>12.4</td>
<td>17.3</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Percent change in baseline HbA1C &gt; 9%</td>
<td>−1.45 ± 1.46</td>
<td>−1.66 ± 1.45</td>
<td>0.02</td>
</tr>
</tbody>
</table>

a Values are given as means ± SD or percentages unless indicated otherwise. p values reflect comparison with the DPP4i group.

DPP4i = dipeptidyl peptidase-4 inhibitor; HbA1C = hemoglobin A1C; TZD = thiazolidinedione.

Table 3. Multivariate logistic regression of achieving goal hemoglobin A1C when comparing dipeptidyl peptidase-4 inhibitors and thiazolidinedione as the third-line triple-therapy agenta

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4i vs TZD</td>
<td>0.63 (0.56-0.71)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HbA1C &gt; 9%</td>
<td>0.55 (0.42-0.71)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.07 (1.06-1.07)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black vs white</td>
<td>0.84 (0.70-1.00)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hispanic vs white</td>
<td>0.74 (0.66-0.83)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CCI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 vs ≥ 5</td>
<td>0.90 (0.79-1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>3-4 vs ≥ 5</td>
<td>0.85 (0.75-0.97)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

a c-index = 0.724.

CCI = Charlson comorbidity index; CI = confidence interval; DPP4i = dipeptidyl peptidase-4 inhibitor; HbA1C = hemoglobin A1C; TZD = thiazolidinedione.

Table 4. Multivariate logistic regression of achieving goal hemoglobin A1C when comparing dipeptidyl peptidase-4 inhibitors and insulin as the third-line triple-therapy agenta

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio (95% CI)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>DPP4i vs insulin</td>
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<td>0.68</td>
</tr>
<tr>
<td>HbA1C &gt; 9%</td>
<td>0.67 (0.52-0.86)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.07 (1.06-1.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black vs white</td>
<td>0.77 (0.64-0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hispanic vs white</td>
<td>0.64 (0.57-0.72)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CCI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 vs ≥ 5</td>
<td>0.84 (0.73-0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>3-4 vs ≥ 5</td>
<td>0.88 (0.77-1.01)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

a c-index = 0.725.

CCI = Charlson comorbidity index; CI = confidence interval; DPP4i = dipeptidyl peptidase-4 inhibitor; HbA1C = hemoglobin A1C; TZD = thiazolidinedione.
had fallen out of favor likely due to the US Food and Drug Administration Drug Safety Communication regarding rosiglitazone and heart failure as well as other safety risks.16

More recently, an updated 2016 US Food and Drug Administration review concluded that the use of pioglitazone may be linked to an increased risk of bladder cancer.17 Although +TZD use was more effective than +DPP4i in this study, it is important for providers to properly screen patients and only treat appropriate patients in order to minimize the risk of adverse effects such as edema, fractures, heart failure, and bladder cancer, which were not evaluated in this study.18,19

In terms of safety outcomes, there was no statistically significant difference in the frequency of composite hypoglycemic events, including ED visits or hospitalizations, when evaluating the +insulin and +TZD groups compared to the +DPP4i group (Table 2). In terms of weight, the +insulin and +TZD groups had a larger mean change in weight compared to the +DPP4i group.

Systematic reviews and network meta-analyses have previously attempted to determine the most optimal add-on agent to metformin and a sulfonylurea. Gross et al10 concluded that there was no clear difference in benefit compared to placebo when adding a third agent for patients who had not achieved glycemic goals while taking metformin and a sulfonylurea. McIntosh et al11 concluded that third-line agents for treatment of T2D have similar glycemic control but vary in their tendency to cause weight gain or hypoglycemia. Our study had a larger sample size, and it focused on the comparative effectiveness and safety of specific drug classes (DPP4i, TZD, insulin) and was able to detect a difference.

Major recommendation changes were made to the ADA Standards of Medical Care in Diabetes in 2018 and 2019, notably for patients with established atherosclerotic cardiovascular disease or chronic kidney disease who may benefit from treatment with a sodium-glucose cotransporter 2 inhibitor or GLP1RA. However, for patients without these comorbidities and for whom cost is a major issue, a sulfonylurea or TZD can still be used as second or third add-on agents to metformin per the 2019 ADA Standards of Medical Care in Diabetes. This recommendation is in line with one of the treatment arms of our study. Considering that cost of therapy is a true concern for patients with diabetes, there is value in the applicability of the results of this study for these patients.20,21

This study has several strengths. This real-world study evaluated a large sample size population, accounting for real-world practice and variations in diet, lifestyle, and medication compliance. Multiple variables with significant clinical impact were taken into consideration, and several methods of data analyses were utilized with similar results, which adds to the robustness of the outcomes. Propensity score matching was used to match the control and treatment groups, adjusting for confounding factors and reducing the risk for bias. Since Kaiser Permanente is an integrated health care system that allows collaboration between health care members, the system can easily collect and analyze patient outcomes, laboratory data, and prescription information for all patients.

This study has some limitations. Since this is a retrospective analysis, covariates such as medication adherence, optimization of sulfonylurea and TZD therapy, and insulin titration were not controlled. This assumed that the clinician intensified therapy following the different guidelines available during the study period from 2006 to 2016. However, we did not expect a difference among study groups, since education regarding diet and lifestyle modifications is standardized within the organization. Selection bias also cannot be ruled out because there may be additional considerations or unobserved variables when selecting the appropriate third-line agent. For example, we did not examine the renal function of patients evaluated in the study. However, the third-line agents evaluated in this study (insulin, TZD, and DPP-4i) can be used for patients with renal impairment. The use of propensity score matching minimized differences using observable variables.

Chart reviews were not performed to validate hypoglycemic events for both the study and control groups; hence, hypoglycemic events were only counted if they were the primary diagnosis. Mild cases of hypoglycemia may not be well documented in the electronic medical record; thus, our study was not able to capture these results. Moreover, patients are usually able to self-manage mild cases of hypoglycemia without incurring additional health care resources. In addition, the goal HbA1C cutoff was based solely on age, not comorbidities. To remedy this, the CCI was evaluated, which predicts the 1-year mortality for a patient who may have a range of comorbid conditions such as heart disease and cancer. For this analysis, the +DPP4i, +insulin, and +TZD groups had a similar CCI score.

Another limitation is that the primary outcomes were surrogate markers, which lack information on long-term outcomes such as microvascular or cardiovascular events. Furthermore, this study was conducted in a large managed care setting, which may limit the applicability of these results to other practice settings. Despite these limitations, given the large sample size, this study reflects real-world practice and can help guide clinicians in decision making.

In the future, additional studies to evaluate the impact of race or ethnicity may be helpful to address the diverse T2D population. Studies with longer follow-up periods may show the long-term effectiveness of these drugs as third-line agents in the treatment of T2D.
CONCLUSION

Although the previous ADA and AACE/ACE guidelines prior to 2018 recommended metformin as first-line therapy, no specific recommendations for second- and third-line agents were made at that time. Not only did clinicians need to consider expected HbA1C reduction and the proportion of patients achieving goal HbA1C, Insulin may be more effective in patients with a baseline HbA1C greater than 9% when evaluating HbA1C reduction. TZD was more effective than DPP4i as a third-line oral agent when evaluating both HbA1C reduction and proportion achieving goal HbA1C. Clinicians should consider the effectiveness and safety of glucose-lowering medications when determining the most optimal triple-therapy regimen.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Authors’ Contributions

Vittoria Marie Ledesma, PharmD, BCPS, Rita L Hui, PharmD, MS, and Fang Niu, MS contributed the study design and concept, with assistance from Natalie Aboubechara, PharmD, BCPS, and Mirta Millares, PharmD, FCSPH, FASHP. Rita L Hui and Fang Niu were responsible for data collection. Vittoria Marie Ledesma, Rita L Hui, and Fang Niu, along with Natalie Aboubechara, interpreted the data. Natalie Aboubechara, Vittoria Marie Ledesma, and Rita L Hui wrote the manuscript, with assistance from Susan M Lee, PharmD, BCPS, Fang Niu, Yesha A Patel, PharmD, BCPS, and Mirta Millares. All authors reviewed and edited the final manuscript. All authors have given final approval to the manuscript.

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