Odds of Acute Kidney Injury in Patients Receiving Dipeptidyl Peptidase 4 Inhibitors: A National Cohort Study Within the Department of Veterans Affairs

S. Scott Sutton1,2,* , Joseph Magagnoli1,2, Tammy H. Cummings2 and James W. Hardin2,3

Preclinical and clinical data of dipeptidyl peptidase 4 (DPP-4) inhibitors have demonstrated discordant data regarding acute kidney injury (AKI). Therefore, we aimed to evaluate the association between DPP-4 use and AKI. This cohort study utilized data from the Department of Veterans Affairs evaluating patients diagnosed with type 2 (T2) diabetes with a DPP-4 inhibitor and compared with nondiabetic and diabetic patients. The primary end point is the development of AKI, and statistical analyses were performed to examine the association. DPP-4 use is associated with a lower odds of AKI compared with diabetics (adjusted odds ratio (OR) = 0.39; 95% confidence interval (CI) = 0.32–0.48) and nondiabetics (OR = 0.64; 95% CI = 0.52–0.79). DPP-4 use in patients with T2 diabetes mellitus is associated with lower odds of AKI within 120 days compared with nondiabetic and diabetic controls when adjusting for study covariates.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✔ Because the dipeptidyl peptidase 4 (DPP-4) enzyme is expressed on non-glucagon-like peptide-1 cell types, nondiabetes medication effects of the DPP-4 inhibitors are possible. Preclinical and clinical data for DPP-4 inhibitors have demonstrated a nephroprotective effect; however, clinical data have also demonstrated that DPP-4 inhibitor use was associated with a higher risk of hospitalization for acute kidney injury (AKI).

WHAT QUESTION DID THIS STUDY ADDRESS?
✔ The purpose of this study is to evaluate patients with type 2 diabetes mellitus with a prescription for a DPP-4 inhibitor vs. diabetic and nondiabetic patients and the associated odds for developing AKI. Research question: What are the odds of AKI in patients with diabetes receiving DPP-4 inhibitors compared with diabetics not receiving DPP-4 inhibitors and nondiabetics?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
✔ This study used a large nationwide cohort of US Veterans to examine the association of AKI between DPP-4 inhibitors and matched control patients. This study adds additional literature to previous published discordant results.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
✔ This study can assist prescribers and payers in understanding real-world experience with this medication. There were lower odds of AKI in the DPP-4 cohort compared with the diabetic and nondiabetic controls when using adjusted models. However, future research should be considered in understanding the risks and benefits of DPP-4 use and the occurrence of AKI.

Diabetes affects more than 29 million people in the United States, and the majority of diabetes cases are type 2 diabetes mellitus (T2DM).1 Diabetes is a risk factor for acute kidney injury (AKI), and AKI episodes may lead to electrolyte abnormalities, pulmonary edema, chronic kidney disease, and cardiovascular complications.2–4 Dipeptidyl peptidase 4 (DPP-4) inhibitors are a class of oral hypoglycemic medications that are used to manage patients with T2DM.5–8 DPP-4 is an enzyme expressed on the surface of most cell types that deactivates bioactive peptides, including glucagon-like peptide-1 (GLP-1). DPP-4 inhibitors affect glucose control through enhancement of glucose-dependent insulin secretion, slowed gastric emptying, and reduction of postprandial glucagon and of food intake. DPP inhibitors are utilized as adjunctive drug therapy or monotherapy for patients inadequately controlled or who cannot take/tolerate other oral diabetes medications. Because the DPP-4 enzyme is also expressed on non-GLP-1 cell types, nondiabetes medication effects of the DPP-4 inhibitors are possible. For example, DPP-4 is also bound on the kidney
proximal tubular cell, and microvesicle-bound DPP-4 secreted from tubular epithelial cells is found in the urine and may be an early marker of kidney damage. Additionally, renal effects of DPP-4 inhibitors may be mediated by increased GLP-1 levels. In addition to the pancreas, the GLP-1 receptor is expressed in glomerular endothelial cells, and renal effects of DPP-4 inhibitors are, in part, mediated by GLP-1 levels. However, the exact role and importance of the mechanism of kidney effects relating to the DPP-4 enzyme or DPP-4 inhibitors are not completely understood. Preclinical and clinical data for DPP-4 inhibitors have demonstrated a nephroprotective effect. However, there have also been clinical data that demonstrated DPP-4 inhibitor use was associated with a higher risk of hospitalization for AKI. The discordant study results warrant the need for more research evaluating DPP-4 inhibitors and AKI. Therefore, the purpose of this study is to evaluate patients with T2DM with a prescription for a DPP-4 inhibitor vs. diabetic and nondiabetic patients and the associated odds for developing AKI within the Department of Veterans Affairs (VA) Veterans Health Administration system.

METHODS

Data

This retrospective cohort study was conducted using data from the Department of Veterans Affairs. The Veterans Affairs Informatics and Computing Infrastructure was utilized to obtain individual-level information on demographics, administrative claims, and pharmacy dispensation. The completeness, utility, accuracy, validity, and access methods are described on the VA website, http://www.virec.research.va.gov. The study was conducted in compliance with the Department of Veterans Affairs’ requirements and received institutional review board and research and development approval. The study utilized diagnosis International Classification of Disease 9th revision (ICD-9-CM) data from October 1999 to September 2015, laboratory data from January 2001 to June 2016, and pharmacy data from December 1999 to June 2016.

Cohort selection

Cases were defined as patients who were diagnosed with T2DM (during October 1999 to September 2015) and had a prescription for a DPP-4 inhibitor (including sitagliptin, saxagliptin, or linagliptin) between the dates June 2005 and February 2016. The study index period for the DPP-4 cases was the earliest date the patient was on a DPP-4 and had an estimated glomerular filtration rate (eGFR) laboratory measure. The eGFR is a calculated laboratory from the patients’ medical record and was captured via claims data by Logical Observation Identifiers Names and Codes code 33914. Nondiabetic controls were defined as patients who never had an ICD-9-CM diagnosis of T2DM and never had an A1c laboratory result. Uncontrolled blood sugar was defined as an A1c value ≥7 for the nondiabetic controls. Diabetic non-DPP-4 controls were defined as those who had a diagnosis of T2DM but never had a prescription for a DPP-4 inhibitor. To ensure adequate medical surveillance and baseline kidney function, patients who never had an eGFR measure while on a DPP-4 were excluded. Furthermore, controls who never had an eGFR laboratory result during the study, June 2005 to February 2016, were excluded.

Matching

A matching algorithm was utilized that matched DPP-4 cases to controls. A variable number of matched controls per case was utilized, with one control being the minimum and seven controls as a maximum. Controls were exact matched on age at index, race, sex, and constrained controls to be within 10 mL/minute of baseline eGFR. Control baseline eGFR measures were also required to be in the same month and year as their matched case.

AKI outcome

Cases and controls were followed from index to 120 days or AKI incident, whichever occurred first. Specifically, AKI was identified from an outpatient acute kidney diagnosis using ICD-9-CM: values were 584 (acute kidney failure), 584.5 (acute kidney failure with lesion of tubular necrosis), 584.6 (acute kidney failure with lesion of renal cortical necrosis), 584.7 (acute kidney failure with lesion of renal medullary necrosis), 584.8 (acute kidney failure with other specified pathological lesion in kidney), and 584.9 (acute kidney failure, unspecified).

Study variables

In addition to our primary predictor (DPP-4 inhibitor use), covariates were utilized to account for possible differences in demographic, disease burden, pharmacy, and laboratory results between the cohorts. Demographic variables included age, sex, and race coded as white, black, other/unknown. The Charlson comorbidity index was utilized to account for differences in disease burden. The Charlson index utilizes all outpatient claims for the 1 year preceding the study index. Additionally, other pharmacy medications were evaluated and included metformin use during the follow-up period, nonsteroidal anti-inflammatory drugs (NSAIDs), and proton pump inhibitors (PPIs).

Statistical analysis

The statistical analysis occurred in two steps. The initial step utilized statistical tests to compare baseline characteristics between the DPP-4 and control cohorts. For continuous variables, such as age, eGFR, and the Charlson comorbidity index, we utilized the F-test from the analysis of variance results. All categorical variables were analyzed using the χ² test. In the second step, we estimated logistic regression models to examine the association between DPP-4 use and AKI. We estimate three models: (i) unadjusted, with only the treatment indicator (diabetic DPP-4, diabetic non-DPP-4, and nondiabetic); (ii) a second adjusted for the Charlson index; and (iii) a model with all covariates (which included treatment indicator, Charlson index, baseline eGFR, uncontrolled A1c, sex, race, age, PPI use, NSAID use, metformin use, and index year). Unadjusted odds of AKI within 120 days for comparisons between cohort groups using a Bonferroni multiplicity adjusted interval were also tested for each model in this step. All data management and matching was done with SAS enterprise guide 7.1 (SAS Institute Cary,
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RESULTS

A total of 363,873 patients met all the study criteria. Of these, 250,269 patients made up the nondiabetic control group, 77,722 the diabetic non-DPP-4 group, and 35,882 the DPP-4 inhibitor cohort. Table 1 displays the summary statistics for the three cohorts. The DPP-4 and control cohorts are clinically similar in terms of age (66.7 (10.1) vs. 66.8 (9.9) vs. 66.5 (10.2)), race (68% white), and sex (96% men). The DPP-4 cohort, on average, has a lower eGFR measure at index (69.5 (24.4) vs. 69.8 (23.3) vs. 72.2 (22.9) mL/minute). The diabetic non-DPP-4 control group, on average, had a higher Charlson index (2.8 (2.3) vs. 2.5 (1.9) vs. 0.8 (1.5)) compared with the diabetic DPP-4 cases and nondiabetic controls. Approximately 56% of the DPP-4 cohort had an uncontrolled A1C (defined as A1c ≥ 7) at baseline, and 55% were on metformin during the follow-up period. Additionally, 14% of the DPP-4 and diabetic non-DPP-4 cohorts and 13% of the nondiabetic control cohort had a prescription for NSAIDs, whereas 32% of both DPP-4 and diabetic non-DPP-4 cohorts and 21% of the nondiabetic controls had a prescription for PPIs. Of the patients on a DPP-4 inhibitor, 61.8% of patients had a prescription for saxagliptin, 44.8% had a prescription for sitagliptin, and 12.9% had a prescription for linagliptin. Patients may have had a prescription for more than one DPP-1, and as a result, the percentages do not sum to 100.

Table 2 presents the occurrence of AKI within 120 days for each cohort. The DPP-4 cohort had 274 incidents of AKI equaling 7.63 (95% confidence interval (CI) = 6.74–8.52) per 1,000 people, the diabetic non-DPP-4 cohort had 21,784 incidents of AKI at 22.95 (95% CI = 21.98–24.04) incidents per 1,000 people, and the nondiabetic cohort had 1,786 incidents of AKI equaling 7.13 (95% CI = 6.80–7.45) incidents per 1,000 people.

The unadjusted logistic regression (Table 3, model 1) demonstrates that patients with diabetes not on a DPP-4 inhibitor had a 3.05-fold increased odds of AKI compared with diabetics on a DPP-4 within 120 days (odds ratio (OR) = 3.05; 95% CI = 2.69–3.47), whereas there was no

Table 1 Patient characteristics

| Variable       | Diabetic non­DPP­4 | Diabetic DPP­4 | Nondiabetic | P value |
|----------------|---------------------|----------------|-------------|---------|
| Age, mean (SD) | N = 77,722          | N = 35,882     | N = 250,269 | < 0.001 |
| Race           |                     |                |             |         |
| Black          | 13,451 (17.3%)      | 6,009 (16.7%)  | 41,390 (16.5%) | < 0.001 |
| Other/unknown  | 11,274 (14.5%)      | 5,401 (15.1%)  | 38,386 (15.3%) |         |
| White          | 52,997 (68.2%)      | 24,472 (68.2%) | 170,493 (68.1%) | < 0.001 |
| Sex            |                     |                |             |         |
| Male           | 75,220 (96.8%)      | 34,484 (96.1%) | 240,436 (96.1%) | < 0.001 |
| Baseline eGFR, mean (SD) | 69.8 (23.3) | 69.5 (24.4) | 72.2 (22.9) | < 0.001 |
| Charlson index, mean (SD) | 2.8 (2.3) | 2.5 (1.9) | 0.8 (1.5) | < 0.001 |
| Uncontrolled A1c | 23,326 (30.0%) | 20,194 (56.3%) | 0 (0%) | < 0.001 |
| NSAID prescription | 11,013 (14.2%) | 5,064 (14.1%) | 33,682 (13.5%) | < 0.001 |
| PPI prescription | 25,164 (32.4%) | 11,325 (31.6%) | 52,263 (20.8%) | < 0.001 |
| Metformin prescription | 28,222 (36.3%) | 19,742 (55.0%) | 0 (0%) | < 0.001 |
| Index year     |                     |                |             |         |
| 2005           | 15 (0.02%)          | 7 (0.02%)      | 89 (0.03%) | 0.24   |
| 2006           | 27 (0.035%)         | 13 (0.036%)    | 159 (0.064%) |         |
| 2007           | 348 (0.448%)        | 161 (0.449%)   | 1,162 (0.464%) |         |
| 2008           | 1,850 (2.38%)       | 864 (2.41%)    | 6,042 (2.41%) |         |
| 2009           | 2,958 (3.81%)       | 1,367 (3.81%)  | 9,522 (3.805%) |         |
| 2010           | 3,976 (5.12%)       | 1,840 (5.13%)  | 12,852 (5.14%) |         |
| 2011           | 5,901 (7.59%)       | 2,700 (7.53%)  | 18,660 (7.46%) |         |
| 2012           | 8,503 (10.94%)      | 3,926 (10.94%) | 27,086 (10.82%) |         |
| 2013           | 8,377 (10.78%)      | 3,864 (10.78%) | 26,553 (10.61%) |         |
| 2014           | 14,938 (19.22%)     | 6,897 (19.22%) | 48,003 (19.18%) |         |
| 2015           | 25,814 (33.21%)     | 11,923 (33.23%)| 83,993 (33.56%) |         |
| 2016           | 5,015 (6.45%)       | 2,320 (6.47%)  | 16,148 (6.45%) |         |

DPP-4 medication^a
Saxagliptin       –       22,207 (61.8%) –
Sitagliptin      –       16,092 (44.8%) –
Linagliptin      –       4,664 (12.9%) –

DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

^aPercentages do not equal 100 because select patients may have received different DPP inhibitors.
statistically significant difference between the nondiabetic control group and the diabetic DPP-4 users (OR = 0.93; 95% CI = 0.82–1.06). However, the second logistic regression model was adjusted for the Charlson comorbidity index as a covariate and demonstrated that both diabetics not on a DPP-4 inhibitors and nondiabetic controls were associated with a higher odds of AKI within 120 days compared with the diabetics on a DPP-4 (OR = 2.55; 95% CI = 2.24–2.9 and OR = 1.7; 95% CI = 1.49–1.94, respectively). This model also revealed that as the Charlson index increases, the odds of AKI also increase (OR = 1.38; 95% CI = 1.37–1.40).

Additionally, a third logistic regression model was utilized that was adjusted for all study covariates and demonstrates that diabetic non-DPP-4 inhibitors and nondiabetics are associated with a higher odds of AKI within 120 days (OR = 2.78; 95% CI = 2.43–3.17 and OR = 1.32; 95% CI = 1.14–1.53, respectively). Model 3 also demonstrates that (i) higher values of the Charlson comorbidity index were associated with an increase in the odds of AKI (OR = 1.26; 95% CI = 1.24–1.27); (ii) higher baseline eGFR values are associated with a lower odds of AKI (OR = 0.96; 95% CI = 0.96–0.96); and (iii) compared with black patients, both white (OR = 0.76; 95% CI = 0.70–0.83) and other/unknown (OR = 0.60; 95% CI = 0.53–0.68) have a lower odds of AKI.

Table 4 presents the results from the unadjusted odds of AKI within 120 days for comparisons between cohort groups using the Bonferroni multiplicity adjusted interval. When comparing DPP-4 cohort with diabetic non-DPP-4 controls, we found that DPP-4 use was associated with a lower odds AKI (unadjusted OR = 0.33; 95% CI = 0.27–0.4; adjusted OR = 0.34; 95% CI = 0.28–0.42). Comparing the DPP-4 cohort with the nondiabetic controls, we found that the odds of AKI in the DPP-4 cohort was not statistically significantly different in the unadjusted model (OR = 1.07, 95% CI = 0.88–1.3), yet was statistically significant with a lower odds of AKI within 120 days in the adjusted models (OR = 0.59, 95% CI = 0.48–0.71 and OR = 0.64, 95% CI = 0.52–0.79). Finally, in comparing the diabetic non-DPP-4 controls to the nondiabetic cohort, we found that the diabetic non-DPP-4 cohort had higher odds of AKI in both unadjusted (OR = 3.27; 95% CI = 2.96–3.61) and adjusted models (OR = 1.5; 95% CI = 1.34–1.67; OR = 1.86; 95% CI = 1.65–2.1).

Table 2 Occurrence of AKI within 120 days

| Cohort                  | Total AKI | Per 1,000 people (95% CI) |
|-------------------------|-----------|--------------------------|
| Diabetic non-DPP-4      | 1,784     | 22.95 (21.98–24.04)      |
| Diabetic DPP-4          | 274       | 7.63 (6.74–8.52)         |
| Nondiabetic             | 1,786     | 7.13 (6.80–7.45)         |

AKI, acute kidney injury; CI, confidence interval; DPP-4, dipeptidyl peptidase 4.

*Bootstrapped 95% CI.

Table 3 Odds of AKI within 120 days

| Variable                  | Model 1   | Model 2   | Model 3   |
|---------------------------|-----------|-----------|-----------|
| (Intercept)               | 0.01 (0.01–0.01) | 0.00 (0.00–0.00) | 0.38 (0.26–0.55) |
| Diabetic DPP-4 (baseline) |           |           |           |
| Diabetic non-DPP-4        | 3.05 (2.69–3.47) | 2.55 (2.24–2.9) | 2.78 (2.43–3.17) |
| Nondiabetic               | 0.93 (0.82–1.06) | 1.7 (1.49–1.94) | 1.32 (1.14–1.53) |
| Charlson index            | 1.38 (1.37–1.40) | 1.26 (1.24–1.27) | 0.96 (0.96–0.96) |
| Baseline eGFR             |           |           |           |
| Uncontrolled A1c          |           |           |           |
| Sex (female baseline)     |           |           |           |
| Male                      | 1.19 (0.95–1.48) |           |           |
| Race (black baseline)     |           |           |           |
| Other/unknown             | 0.6 (0.53–0.68) | 0.76 (0.7–0.83) |           |
| White                     | 0.98 (0.98–0.99) | 0.71 (0.66–0.77) |           |
| Age                       | 0.58 (0.49–0.68) | 0.41 (0.35–0.48) |           |
| PPI use                   | 0.41 (0.35–0.48) | 0.92 (0.91–0.94) |           |

AKI, acute kidney injury; CI, confidence interval; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.
Rats given an oral dose of DPP-4 sitagliptin (200 mg/kg/day) for 8 weeks had a renoprotective effect on their remnant kidneys.23 Diabetic rats compared with nondiabetic rats treated with a DPP-4 inhibitor (vildagliptin) had lower body weight, plasma insulin levels, and serum creatinine levels. Additionally, the existence of interstitial expansion, glomerulosclerosis, and the thickening of the glomerular basement membrane attenuated renal injury in diabetic rats administered DPP-4 inhibitors.13 DPP-4 inhibition resulted in a dose-dependent protective effect on kidney function in a rat model, as shown by reduced serum creatinine levels after renal ischemia–reperfusion injury. Additionally, the reduced serum creatinine levels were accompanied by morphological protection indicated by a decrease in tubular necrosis.15

Select clinical evaluations have demonstrated consistent results of the preclinical animal studies on the association of AKI with DPP-4 inhibitors. The DPP-4 inhibitor linagliptin was not associated with increased kidney disease risk compared with placebo in individual patient-level data of pooled analysis of 13 phase II or III clinical trials.24 DPP-4 inhibitors were associated with reduced risk of mild and severe forms of AKI among patients with incident diabetes in a nationally representative cohort in Taiwan.25 Additionally, a retrospective cohort study of a large medical and pharmacy claims database demonstrated that there was not an association between the use of sitagliptin and AKI.26 In contrast, there are reports of an increased association of AKI and DPP-4 inhibitors. The US Food and Drug Administration has reported episodes of acute worsening of renal function following exposure to inappropriate doses of sitagliptin in patients with renal insufficiency where there has been inappropriate dose adjustment.27 Additionally, a nested case-control study conducted using Taiwan’s National Health Insurance Research Database demonstrated that those using DPP-4 inhibitors had an increased risk of AKI compared with nonusers.16

Our study results are consistent with the preclinical animal models and clinical studies that demonstrate a protective effect of DPP-4 inhibitor use on AKI. Our study provides value to the current literature regarding DPP-4 inhibitors and AKI because of previous discordant results. We utilized a different patient population to evaluate the external validity and generalizability of previous studies. Our large sample size utilizing matched controls provides additional evidence that DPP-4 inhibitors may have another role in addition to managing patients’ blood glucose levels. Although our study has a significant number of strengths, there are several limitations that are common to claims database studies of like methodology. Because this study was retrospective and observational, unmeasured confounders may have affected the results, despite matching of key covariates between cohorts. For example, there is a significant difference in the utilization of metformin between the DPP4 and non-DPP4 cohorts. Therefore, it is possible the patients on DPP4/metformin could have received more stringent care, and this could have influenced the outcome. The use of antihypertensive medications was not evaluated, and the outcome of blood pressure control through an antihypertensive may have had an influence on renal outcomes. Our study variable was the utilization of a DPP inhibitor and not the dose. However, the dose and/or existing renal function of the patient could have impacted the results. Specifically, the US Food and Drug Administration has reported episodes of acute worsening of renal function following exposure to inappropriate doses of sitagliptin in patients with renal insufficiency where there has been inappropriate dose adjustment.27 Additionally, the study population was predominantly middle-to older-aged white men; therefore, our findings may not be generalizable to patients of different age groups or sexes. Additionally, only the association of DPP-4 inhibitors and AKI were studied; therefore, causality or mechanisms could not be investigated. However, our association data are consistent with previously conducted preclinical studies evaluating mechanisms. Preclinical studies suggest a glomerular and/or tubular mechanism of kidney injury; however, the exact role of glomerular and/or tubular mechanisms, and the role of DPP-4 inhibitors in these mechanisms, requires further investigation.

### Table 4 Odds of AKI within 120 days: Comparisons between cohort groups

| Contrast | Model 1 OR (95% CI) | Model 2 OR (95% CI) | Model 3 OR (95% CI) |
|----------|----------------------|----------------------|----------------------|
| Diabetic DPP-4 vs. diabetic non-DPP-4 | 0.33 (0.27–0.4) | 0.39 (0.32–0.48) | 0.34 (0.28–0.42) |
| Diabetic DPP-4 vs. nondiabetic | 1.07 (0.88–1.3) | 0.59 (0.48–0.71) | 0.64 (0.52–0.79) |
| Diabetic non-DPP-4 vs. nondiabetic | 3.27 (2.96–3.61) | 1.5 (1.34–1.67) | 1.86 (1.65–2.1) |

AKI, acute kidney injury; CI, confidence interval; DPP-4, dipeptidyl peptidase 4; OR, odds ratio.

*Bonferroni multiplicity adjusted interval.
and importance of the mechanism of kidney effects relating to the DPP-4 enzyme or DPP-4 inhibitors is not completely understood. Further research is needed to continue the evaluation of AKI in patients receiving DPP4 inhibitors to further our understanding of the association, mechanisms, and clinical application of AKI episodes.

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