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ORIGINAL ARTICLE

Association Between Use of Dipeptidyl Peptidase-4 Inhibitors and the Risk of Acute Kidney Injury: A Nested Case-Control Study

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Abstract

Objective: To examine the risk of acute kidney injury (AKI) in a nationwide cohort of patients with type 2 diabetes initiating dipeptidyl peptidase-4 (DPP-4) inhibitors.

Patients and Methods: This nested case-control study of a cohort of adult DPP-4 inhibitor users with type 2 diabetes who were hospitalized for AKI between January 1, 2010, and December 31, 2013, was conducted using Taiwan's National Health Insurance Research Database. Each AKI case was matched with one control subject according to duration of follow-up, age, sex, urbanization level, monthly income, comorbidity severity, and well-known predisposing factors for AKI. Odds ratios (ORs) for AKI were calculated according to current, recent, or past use of DPP-4 inhibitors.

Results: A total of 6752 cases with AKI and 6752 matched controls were analyzed. The exposure prevalence of DPP-4 inhibitor use in the previous year was higher among patients with AKI (adjusted OR, 1.20; 95% CI, 1.05-1.36; P=.006). In a stratified analysis, the association was significant for current DPP-4 inhibitor use (adjusted OR, 1.26; 95% CI, 1.08-1.48; P=.004), but not for recent or past use.

Conclusion: In this large contemporary cohort, DPP-4 inhibitor users had an increased risk of AKI development compared with nonusers. Further research is warranted to investigate the mechanism underlying this association.

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Dipeptidyl peptidase-4 (DPP-4) inhibitors, first approved by the US Food and Drug Administration in 2006, are a novel class of oral antidiabetic medications that potentiate the glucose-dependent incretin effect for serum glucose reduction, and therefore are associated with an acceptable risk of hypoglycemia while achieving better glycemic control.[1] At the request of the US Food and Drug Administration, the cardiovascular safety of new antidiabetic therapies has been ascertained since 2008.[2] Based on observational data[3] and the results of recent major clinical trials,[4-7] DPP-4 inhibitors appear to be safe for patients with type 2 diabetes mellitus (T2DM) in terms of cardiovascular events; however, data regarding their renal safety are limited.

The literature contains reports of postmarketing cases of worsening renal function associated with DPP-4 inhibitor use, especially in patients with chronic kidney disease (CKD) and those receiving inappropriate doses of these drugs.[8,9] Although clinical trials often provide high levels of evidence for the causality and safety of medication interventions, they may be underpowered for the evaluation of uncommon outcomes, which requires larger samples with sufficient follow-up time. Thus, we conducted a nationwide nested case-control cohort study using Taiwan's National Health Insurance Research Database (NHIRD) to determine whether the use of DPP-4 inhibitors is associated with an increased risk of acute kidney injury (AKI), compared with nonuse, in patients with T2DM.

METHODS

Data Sources

For this study, we used the Longitudinal Cohort of Diabetes Patients data set, a de-identified secondary database covering most of the T2DM population in Taiwan. This

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data set was extracted from the NHIRD and released by Taiwan's National Health Research Institutes exclusively for research purposes. The NHIRD and Longitudinal Cohort of Diabetes Patients data set have been described in detail[3,10,11] and validated.[12] Briefly, the NHIRD contains information on all hospital admissions, outpatient visits, diagnoses, prescriptions, and procedures for 99.9% of Taiwan's 23 million inhabitants. All disease diagnoses are recorded according to the *International Classification of Disease, Ninth Revision, Clinical Modification* (*ICD-9-CM*).

Ethics, Consent, and Permissions

The research ethics committee of Taipei City Hospital approved the study protocol (TCHIRB-10404107-W).

Setting and Participants

Because DPP-4 inhibitors became widely available in Taiwan in March 2009, we identified in the Longitudinal Cohort of Diabetes Patients data set 20 years or older persons with T2DM who were prescribed these drugs between January 1, 2010, and December 31, 2013. Patients were followed until the study outcome of hospitalization for AKI, death, or December 31, 2013, whichever occurred first.

In the cohort, *cases* were defined as patients hospitalized with a principal diagnosis of AKI (*ICD-9-CM* 584.x) during the study period. The diagnostic accuracy of AKI records in this database has been validated.[13,14] To enable the greatest degree of comparability with ongoing research based on US and UK databases, we used the screening algorithm for hospitalization for AKI proposed by Lo Re et al.[15] The index date was the first date of hospitalization for AKI. Given that diabetic patients may be misdiagnosed with AKI because of progressive CKD in essence, we excluded patients with histories of CKD (*ICD-9-CM* 585.x) or hospitalization within 365 days before the index date, as well as kidney transplant recipients, to minimize potential confounding of AKI risk estimates. Individuals without AKI were included in the control pool, and the same exclusion criteria were applied. For each case, 1 individual in the control pool who remained follow-up as cases occurred was randomly selected as a control after matching on duration of follow-up (cohort entry to index date), age (±5 years), sex, urbanization level, monthly income, Charlson Comorbidity Index score,[16] adapted Diabetes Complications Severity Index score,[17,18] duration of T2DM (±6 months), and predisposing factors for AKI, including hypertension, peripheral arterial disease, heart failure, liver disease, and dyslipidemia.

Exposure Definition

Cases and controls were allocated to 2 mutually exclusive categories based on exposure to DPP-4 inhibitors (including sitagliptin, vildagliptin, and saxagliptin) before the occurrence of AKI. For each DPP-4 inhibitor prescription, we collected detailed information on drug type, quantity, dosage, date of prescription, and days of drug supply. All data regarding DPP-4 inhibitors prescribed within 365 days before the index date were extracted. The timing of each DPP-4 inhibitor use before the index date was determined by the end of the last-dispensed drug supply. DPP-4 inhibitor use was further classified into 3 groups on the basis of timing with regard to the AKI index date: (1) current use (≤30 days before the index date), (2) recent use (31-90 days before the index date), and (3) past use (91-365 days before the index date).

Sensitivity Analyses

The primary exposure of interest was DPP-4 inhibitor therapy. However, to determine whether observed differences in the risk of AKI could be explained fully from confounding by indication, we performed sensitivity analyses that considered the use of other oral antidiabetic drugs (including metformin, sulfonylurea, alpha-glucosidase inhibitors, and thiazolidinedione) as a comparator with indications similar to those of DPP-4 inhibitors.

The demographic characteristics of cases and controls were compared using chi-square tests for categorical variables and independent *t* tests for continuous variables. Odds ratios (ORs) were used to compare exposure to DPP-4 inhibitors between cases and controls. We used a conditional logistic regression model to adjust for oral antidiabetic drugs, insulin use, and all other potential confounders with *P* less than .05 in the univariate analysis, including nonsteroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme

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