JAMDA 17 (2016) 59–64

JAMDA

journal homepage: www.jamda.com

Original Study

Cardiovascular Outcomes of Dipeptidyl Peptidase-4 Inhibitors in Elderly Patients With Type 2 Diabetes: A Nationwide Study

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Keywords:
Dipeptidyl peptidase-4 inhibitor
elderly
diabetes mellitus
major adverse cardiovascular events
mortality

A B S T R A C T

Objectives: The elderly (aged ≥65 years) population with type 2 diabetes (T2D) is growing substantially, but evidence for associations between the use of dipeptidyl peptidase-4 inhibitors (DPP-4is), novel incretin-based antidiabetic drugs, and clinical hard endpoints in this group remains inconclusive. We aimed to assess the safety and cardiovascular effects of DPP-4i use in a nationally representative sample of elderly adults with T2D.

Design, setting, and participants: We conducted a nationwide, observational, propensity score–matched study using Taiwan's National Health Insurance Research Database. Of a total of 414,213 patients aged ≥65 years with T2D, 58,485 patients receiving initial DPP-4i prescriptions between March 1, 2009, and June 31, 2013, were included. Each DPP-4i user was matched with a nonuser control using propensity scores. The endpoints were all-cause mortality and major adverse cardiovascular events (MACEs), including ischemic stroke and myocardial infarction. Potential adverse effects of hospitalization for heart failure and hypoglycemia were also evaluated.

Results: Compared with the matched control cohort, the risks of all-cause mortality (hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.52–0.56), MACEs (HR 0.79, 95% CI 0.75–0.83), myocardial infarction (HR 0.79, 95% CI 0.72–0.87), and ischemic stroke (HR 0.79, 95% CI 0.75–0.84) were lower in the DPP-4i cohort. DPP-4i use did not affect the risks of hospitalization for heart failure and hypoglycemia. Stratified analyses produced consistent results across age, sex, and comorbidity subgroups.

Conclusions: Prescription of DPP-4is was associated with reduced risks of all-cause mortality and MACEs in patients aged ≥65 years with T2D.

Type 2 diabetes (T2D) affects more than 25% of US adults aged 65 years or older, and the affected population reached 11.2 million at the end of 2012.[1] The number of patients aged 65 or older with T2D is estimated to double to 26.7 million by 2050[2] because of the combined effects of population aging and increasing rates of overweight and obesity.[3]

The treatment of elderly patients with T2D is challenging due to comorbid conditions, frailty, polypharmacy, and age-related decline in pancreatic islet cell function.[4] Drug-induced hypoglycemia (ie, due to the use of sulphonylureas, meglitinides, and insulin) is a major obstacle to the treatment of this condition in elderly patients.[5] The high prevalence of cardiovascular complications in these patients also prohibits the use of thiazolidinediones, which may worsen cardiovascular conditions and cause heart failure.[6] Although metformin use is not associated with hypoglycemia in this population, caution must be taken, especially for patients with unintentional weight loss and renal function decline. These conditions are usually overlooked

The authors declare no conflicts of interest.
C-JS and H-TC contributed equally to the paper.

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http://dx.doi.org/10.1016/j.jamda.2015.10.009
1525-8610/

because low muscle mass may result in "normal" serum creatinine levels. In addition, the optimal target of glycemic control in elderly patients with T2D remains controversial.[7] The guidelines of the American Diabetes Association and the European Association for the Study of Diabetes encourage personalized target definition based on life expectancy, health status, and the risk of hypoglycemia, rather than the use of glycated hemoglobin (HbA1c) values alone to guide treatment, as in younger and/or healthier populations.[8]

Nevertheless, the guidelines are not sufficiently clear and concrete to be easily adapted in clinical practice because of the lack of strong evidence, as older and/or frail patients with T2D were usually excluded from most randomized controlled trials (RCTs).[9,10] Dipeptidyl peptidase-4 inhibitors (DPP-4is), which are novel incretin-based antidiabetic drugs, thus seem to be an ideal alternative for elderly patients with T2D. The antiglycemic effects of these drugs originate from the increase in insulin levels in a glucose-dependent manner, resulting in little risk of hypoglycemia. Systematic reviews of small RCTs with short-term follow-up periods also have demonstrated that DPP-4i use in elderly patients safely and effectively lowers glucose levels.[11,12] However, data on cardiovascular outcomes of DPP-4i use in older populations with T2D remain limited. Thus, the aim of the present study was to investigate the relationship between DPP-4i use and major adverse cardiovascular events (MACEs) during a long-term follow-up period in patients aged 65 years or older with T2D.

Methods

Data Source

We used Taiwan's National Health Insurance Research Database (NHIRD) for this study. The NHIRD has been described in detail elsewhere[13,14]; it is more extensive than other nationwide research databases.[15] Taiwan's national health insurance program has achieved universal coverage of the population since 1995. Accordingly, the NHIRD contains comprehensive information on medical care, including outpatient visits, emergency room visits, and hospitalizations, with documentation of the relevant diagnostic codes, procedures, and prescriptions, for 23 million inhabitants of Taiwan. Diagnostic codes are based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). The NHIRD was released for exclusively research purposes, and all data it contains have been encrypted to protect individuals' privacy. The Institutional Review Board of Taipei City Hospital exempted this study from full review (TCHIRB-10404107-W) because the data were secondary and de-identified.

Study Cohort

This nationwide observational cohort study included all patients aged 65 years or older with the diagnosis of T2D registered in the NHIRD between March 1, 2009, and June 31, 2013, to ensure the wide availability of DPP-4is (sitagliptin, vildagliptin, saxagliptin, and linagliptin) in Taiwan's market during the study period. The accuracy of T2D diagnoses in the NHIRD has been validated.[16] According to DPP-4i prescription during the observation period, patients were classified as DPP-4i users and nonusers (matched controls). We extracted all relevant data for DPP-4i prescriptions, including drug type, quantity, dose, dispensing date, and days of drug supply. The first date of DPP-4i prescription was defined as the index date. An index date was assigned randomly to each DPP-4i nonuser according to the corresponding index date for a DPP-4i user. The mean compliance rate was measured by the proportion of DPP-4i pill-days covered during the interval from the index date until death or December 31, 2013, whichever occurred first.[17] Insufficient compliance with DPP-4i treatment was defined as fewer than 80% of days covered.[18]

Propensity Score Matching

For all DPP-4i users and nonusers, we calculated propensity scores to estimate the probability of DPP-4i use using a logistic regression model with the following covariates: year of index date, month of index date, age, sex, monthly income, urbanization level, Charlson Comorbidity Index score,[19] number of outpatient visits to metabolism and endocrinology professionals in the past year, adapted Diabetes Complications Severity Index (aDCSI) score,[20] duration of T2D, other concomitant medications (other antidiabetic drugs, antihypertensive drugs, aspirin, clopidogrel, ticlopidine, nonsteroidal anti-inflammatory drugs, and statins), and baseline major comorbidities. We attempted to match each patient in the DPP-4i cohort with a patient in the control cohort with a similar propensity score, based on nearest-neighbor matching without replacement, using a caliper width equal to 0.1 of the standard deviation of the logit of the propensity score.

Outcomes

The primary outcomes were all-cause mortality and MACEs, a composite measure of hospitalization for ischemic stroke (ICD-9-CM code 433.x, 434.x, or 436) and myocardial infarction (ICD-9-CM code 410.x). The accuracy of stroke and myocardial infarction diagnoses recorded in the NHIRD has been validated.[21,22] The secondary outcomes were hospitalization for heart failure (ICD-9-CM code 428.x) and hypoglycemia (ICD-9 CM code 251.0x, 251.1x, or 251.2x). All participants were followed until death or December 31, 2013.

Statistical Analysis

We calculated summary descriptive statistics for the study cohort using baseline demographic and clinical variables. We used standardized differences to check for balance between the DPP-4i and matched control cohorts. Propensity scores for the likelihood of DPP-4i use were calculated by multivariate logistic regression analysis, conditional on baseline covariates (Supplementary Table 1). The incidence rates of outcomes of interest in the 2 cohorts were calculated using Poisson distribution. Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risks of outcomes of interest in each group. Because of the high mortality rate in elderly patients, competing-risks regression using Fine and Gray's model was also performed.[23] The likelihood ratio test was used to examine the interaction between DPP-4i use and the following covariates: age, sex, hypertension, heart failure, myocardial infarction, cerebrovascular disease, and drug adherence. Subgroup Cox regression analyses were performed accordingly. The SQL Server 2012 (Microsoft Corporation, Redmond, WA) was used for data linkage, processing, and sampling. Propensity scores were calculated using SAS version 9.3 (SAS Institute, Cary, NC). All other statistical analyses were conducted with STATA statistical software (version 12.0; StataCorp, College Station, TX). Statistical significance was defined as $P < .05$.

Results

Characteristics of the Study Population

A total of 414,213 patients aged 65 years or older with T2D registered between March 2009 and June 2013were included in the analysis. Demographic information for the patient population is summarized in Table 1. During the observation period, 14.1% (n = 58,485) of patients were treated with DPP-4is. Most (53.8%) of DPP-4i users were women, and the mean age was 74.3 ± 5.9 years. The median aDCSI score in this cohort was 4, and the median duration of