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ORIGINAL ARTICLE

Outcomes for Inappropriate Renal Dose Adjustment of Dipeptidyl Peptidase-4 Inhibitors in Patients With Type 2 Diabetes Mellitus: Population-Based Study

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Abstract

Objectives: To estimate inappropriate dosing of dipeptidyl peptidase-4 (DPP-4) inhibitors and to assess the risk of emergency department visits, hypoglycemia, and mortality in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) prescribed inappropriate DPP-4 inhibitor doses because limited real-world information is available regarding rates of DPP-4 inhibitor dose adjustment and its safety in patients with T2DM and CKD.

Patients and Methods: We performed a retrospective observational cohort study of 82,332 patients aged 30 to 75 years with T2DM and CKD being treated with DPP-4 inhibitors from January 1, 2012, through December 31, 2014, using the Korean National Health Information Database. We divided the patients according to the prescription of DPP-4 inhibitor with or without dose adjustment according to estimated glomerular filtration rate. The incidences of emergency department visits, hypoglycemia, and mortality were assessed using hazard ratios estimated using Cox proportional hazards regression modeling.

Results: Approximately 40% of patients with T2DM and CKD were prescribed an inappropriate dose of DPP-4 inhibitor from 2009 through 2011; this proportion decreased to 24.4% in 2015. Hazard ratios (95% CIs) for inappropriate vs appropriate dosing of DPP-4 inhibitors were 1.115 (1.005-1.237) for mortality, 1.074 (1.018-1.133) for emergency department visits, and 1.192 (1.054-1.349) for severe hypoglycemia after multivariable adjustment for confounding factors.

Conclusion: One of every 3 patients with T2DM and CKD received inappropriate dosing of DPP-4 inhibitor, which was associated with high risk of emergency department visits, severe hypoglycemia, and mortality.

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The prevalence of diabetes in Koreans 30 years and older increased steadily from 5.6% in 2006 to 8.0% in 2013.[1] Complications associated with diabetes have increased concomitantly; 38.8% of patients with end-stage renal disease were found to have type 2 diabetes mellitus (T2DM), and 1.2% of patients with T2DM had end-stage renal disease.[2,3] The prevalence of chronic kidney disease (CKD) in patients with T2DM was 27.3% according to the Korean National Health and Nutritional Examination Survey 2011-2013.[4] In patients with T2DM, the presence of CKD markedly increases cardiovascular risk and mortality.[5-7] In addition, in people with T2DM, CKD is a significant risk factor for the development of hypoglycemia.[8,9]

Clearance of many drugs decreases with decreasing kidney function, and this results in prolonged exposure to higher levels of the drug or its metabolites and potentially adverse effects. Patients with moderate to severe CKD (stages 3-5) are at greatest risk for this occurrence. According to the Korean Diabetes Fact Sheet 2015, metformin

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accounted for 80.4% of total prescriptions in 2013, and sulfonylurea accounted for 58.5%. The use of dipeptidyl peptidase-4 (DPP-4) inhibitors has increased dramatically since 2008 and accounted for one-third of the market share (38.4%) in 2013.[10] The dosage of most of the frequently prescribed antidiabetic medications, including metformin, sulfonylurea, and some kinds of DPP-4 inhibitors, should be adjusted in patients with T2DM according to the degree of CKD, so choosing the correct antidiabetic medications is a challenge in treating patients with T2DM and CKD. Some types of DPP-4 inhibitors, such as sitagliptin, saxagliptin, and vildagliptin, require dose reduction in patients with renal impairment because of their predominantly renal route of excretion, but other types of DPP-4 inhibitors (eg, linagliptin) are exempt from dose adjustment because they are excreted via the enterohepatic system.

Limited real-world information is available regarding rates of dose adjustment and the safety of dose adjustment in patients with T2DM and CKD. The objectives of this study were to estimate the level of inappropriate dosing with DPP-4 inhibitors and to assess the risk of death, emergency department (ED)visits, and severe hypoglycemia according to appropriate and inappropriate doses of DPP-4 inhibitors in patients with T2DM and CKD.

METHODS

Study Database

Data for the analysis were from the National Health Information Database (NHID), which is a public database on health care utilization and health screening that contains sociodemographic and mortality information for the entire population of South Korea. The NHID contains data for 2002 through 2015. The NHID, which is produced by the National Health Insurance Service, was launched by integrating 375 insurance associations in 2000 and provides longitudinal data for 97% of the Korean population, with linkage to the National Death Registry[11,12] and the national health screening program. This insurance claims database includes inpatient and outpatient information, including age, sex, *International Classification of Diseases, 10th Revision, Clinical Modification* diagnostic codes, length of stay, treatment costs, services received, and the prescription record (drug code, days prescribed, daily dosage). The national health screening program was initiated in 2009 and includes a medical interview and postural examination, chest radiography, blood test, urine test, and dental screening, among others.[11] Serum creatinine data became available after 2009, and eGFR estimation was standardized by the Modification of Diet in Renal Disease (MDRD) equation after 2012; therefore, this study was conducted from January 1, 2012, through December 31, 2014. Approval was obtained from the institutional review board of Kangbuk Samsung Hospital for the study protocol.

Patient Selection and Procedures

This was a national observational cohort study that included 82,332 patients aged 30 to 75 years with T2DM and CKD who were prescribed DPP-4 inhibitors from January 1, 2012, through December 31, 2014. From January 1, 2012, through December 31, 2014, 22,692,503 individuals participated in the national health screening program. Of these, the following individuals were excluded: age younger than 30 years or older than 75 years, eGFR determined not by MDRD equation, eGFR lower than 15 mL/min per 1.73 m^2 or higher than 60 mL/min per 1.73 m^2, absence of diabetes, absence of DPP-4 inhibitor prescription within 1 year after the national health screening program, missing data, history of end-stage renal disease, or death within 1 year after the national health screening. Finally, the total number of eligible participants in this study was 82,332. Chronic kidney disease was defined based on the eGFR, which is based on the serum creatinine level. The eGFR was calculated using the MDRD GFR equation: $GFR = 186 \times (\text{Serum Creatinine})^{-1.154} * (\text{age})^{-0.203} * 0.742$ (if female).[13] A patient's degree of CKD was assigned according to the definitions of the National Kidney Foundation. We examined the following groups of patients on the basis of CKD: moderate CKD (stage 3;

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eGFR, 30-59 mL/min per 1.73 m^2) and severe CKD (stage 4; eGFR, 15-29 mL/min per 1.73 m^2). The DPP-4 inhibitors were selected according to the Anatomical Therapeutic Chemical Classification System; codes A10BH04+A10BD13 (alogliptin), A10BH91 (anagliptin), A10BH06+A10BD18 (gemigliptin), A10BH05+A10BD11 (linagliptin), A10BH03+A10BD10 (saxagliptin), A10BH01+A10BD07 (Sitagliptin), A10BH90 (teneligliptin), and A10BH02+A10BD08 (vildagliptin) were considered. Appropriate or inappropriate dosing with DPP-4 inhibitors was defined based on the daily dose of DPP-4 inhibitor, the patient's eGFR, and the manufacturer's guidelines. To allow adequate follow-up time to address the research questions and ensure that any observed absence of health care events was due to true medical inactivity rather than cessation of care, patients were required to have 12 months of continuous post−index date data. The index date was defined for each patient as the date of the first prescription or pharmacy dispensation for any DPP-4 inhibitor. Treatment initiation episodes were defined as prescription/filling of a prescription for any DPP-4 inhibitor.

Outcomes

Outcomes were all-cause death as well as ED visits and severe hypoglycemia. All-cause death was defined according to the National Death Registry. Emergency department visits were defined according to the emergency medical care charge code (AC101-AC105), which is necessary to claims for emergency management regardless of diagnosis and hospitalization. Severe hypoglycemia was defined as an ED visit due to hypoglycemia (*International Classification of Diseases, 10th Revision, Clinical Modification* codes E1163, E1263, E1363, E1463, and E16.x).

Data Analyses

Baseline characteristics were analyzed using descriptive statistics. Categorical variables are described as frequencies and percentages and continuous variables as mean ± SD. We compared baseline characteristics of participants who received appropriate or inappropriate doses of DPP-4 inhibitors. Continuous variables were compared using the Student *t* test, and categorical variables were compared using the χ^2 test. According to appropriate or inappropriate dosing with DPP-4 inhibitors, incidences of outcomes were estimated using the total follow-up period for death, number of ED visits, and number of severe hypoglycemia episodes. Survival curves were estimated using the Kaplan-Meier method, and the log-rank test was also conducted. All outcome analyses were stratified according to appropriate or inappropriate dosing with DPP-4 inhibitors by Cox proportional hazards regression analysis while controlling for baseline covariates. Hazard ratios (HRs) and 95% CIs are reported for outcomes. Inappropriate dosing effects in subgroups defined based on eGFR and other antidiabetic medications and potential interactions were evaluated by Cox proportional hazards regression analyses, and results are presented in a forest plot. We deemed a 2-tailed $P<.05$ to be significant. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc) and R programming, version 3.4.1 (The R Foundation for Statistical Computing).

RESULTS

We first analyzed the level of inappropriate dosing with DPP-4 inhibitors from January 1, 2009, through December 31, 2015. Prescriptions of DPP-4 inhibitors to patients with T2DM increased by 11.6-fold (from 50,191 persons to 580,443 persons) during this period. At the same time, prescription of DPP-4 inhibitors to patients with T2DM with a GFR less than 60 mL/min per 1.73 m^2 increased similarly by 10.9-fold (from 6344 persons to 69,109 persons). The proportion of patients with T2DM and CKD who received inappropriate doses of DPP-4 inhibitors was approximately 40% from 2009 through 2011. This proportion decreased starting in 2012 and reached 24.4% in 2015; at the same time, the use of new DPP-4 inhibitors (eg, linagliptin and gemigliptin) that do not require dosage adjustment in any stage of CKD increased starting in 2012 (Supplemental Figures 1 and 2, available online at http://www.

mayoclinicproceedings.org). However, the proportion of inappropriate dosing with DPP-4 inhibitors that do require dosage adjustment did not change in the same period (Supplemental Figure 1).

Characteristics of Inappropriate and Appropriate Dosing DPP-4 Inhibitor Groups

Of 82,332 persons, 21,559 (26.2%) were prescribed inappropriate dosing of DPP-4 inhibitor. Several differences were noted between patients receiving an inappropriate dose of DPP-4 inhibitors and those receiving an appropriate dose (Table1). There were slightly fewer male than female patients in the inappropriate dosing group (46.8%), whereas there were slightly more male than female patients in the appropriate dosing group (51.0%) ($P<.001$). Patients in the inappropriate dosing group were older (mean ± SD age: 64.73±7.65 years vs 64.28±7.67 years; $P<.001$); had lower mean ± SD diastolic blood pressure (76.5±10.0 mm Hg vs 76.9±9.9 mm Hg; $P<.001$), glucose level (139.71±49.17 mg/dL [7.75±2.73 mmol/L] vs 141.62±48.55 mg/dL [7.86±2.69 mmol/L]; $P<.001$), and eGFR (48±8.77 mL/min per 1.73 m^2 vs 52.6±8.07 mL/min per 1.73 m^2; $P<.001$); and had a higher mean ± SD total cholesterol level (179.24±43.16 mg/dL [4.64±1.12 mmol/L] vs 178.5±41.91 mg/dL [4.62±1.09 mmol/L]; $P<.001$) than those in the appropriate dosing group. Patients in the inappropriate dosing group were also more likely to receive insulin (18.84% vs 16.35%; $P<.001$) and meglitinide (2.09% vs 1.83%; $P=.02$) and less likely to receive sulfonylurea (59.68% vs 63.37%; $P<.001$) and metformin (58.78% vs 64.36%; $P<.001$) than those in the appropriate dosing group.

Associations Between Inappropriate Dosing With DPP-4 Inhibitors and Death, ED Visits, and Severe Hypoglycemia

A total of 1663 deaths occurred overall (529 in the inappropriate dosing group and 1134 in the appropriate dosing group) (Table 2). The incidence of deaths in the appropriate dosing group (14.14 deaths per 1000 person-days; 95% CI, 13.34-14.99 deaths per 1000 person-days) was lower than that in the inappropriate dosing group (17.34 events per 1000 person-days; 95% CI, 15.92-18.88 events per 1000 person-days; log-rank $P<.001$) (Figure 1A), and the HR of inappropriate dosing was 1.149 (95% CI, 1.036-1.275). In multivariable Cox proportional hazards regression modeling, the incidence of death was significantly higher in the inappropriate dosing group than in the appropriate dosing group (adjusted HR=1.115; 95% CI, 1.005-1.237) (Table 2) after adjusting for age, sex, smoking and alcohol drinking status, systolic blood pressure, total cholesterol level, other antidiabetic drug treatment, and history of ED visits or severe hypoglycemia events. Although the incidence of ED visits in the appropriate dosing group (64.52 events per 1000 person-days; 95% CI, 62.73-66.36 events per 1000 person-days) was not different from that in the inappropriate dosing group (66.58 events per 1000 person-days; 95% CI, 63.65-69.66 events per 1000 person-days; log-rank $P=.60$) (Figure 1B), the incidence of severe hypoglycemia and ED visits due to hypoglycemia in the appropriate dosing group (10.24 events per 1000 person-days; 95% CI, 9.55-10.97 events per 1000 person-days) was notably lower than that in the inappropriate dosing group (12.54 events per 1000 person-days; 95% CI, 11.33-13.88 events per 1000 person-days; log-rank $P=.03$) (Figure 1C). Table 2 also shows that the inappropriate dosing group had higher risk of ED visits (HR=1.076; 95% CI, 1.02-1.135) and severe hypoglycemia (HR=1.199; 95% CI, 1.061-1.357) than the inappropriate dosing group after adjusting for age, sex, and history of ED visits or severe hypoglycemia events. These results remained largely unchanged after adjusting for all available confounding factors, including other antidiabetic medications (Table 2).

Subgroup Analyses by CKD Stage

We conducted subgroup analyses stratified by CKD stage 3 (eGFR=30-59 mL/min per 1.73 m^2) and stage 4 (eGFR=15-29 mL/min per 1.73 m^2). Even after adjustment

TABLE 1. Baseline Characteristics of Study Patients With Type 2 Diabetes Mellitus and Chronic Kidney Disease by the Appropriate and Inappropriate Dosing of Dipeptidyl Peptidase-4 Inhibitors, 2012 to 2014

Characteristic	Inappropriate dosing group (n=21,559)	Appropriate dosing group (n=60,773)	*P* value[a]
Age (y), mean ± SD	64.73±7.65	64.28±7.67	<.001
Age group (No. [%])			<.001
30-39 y	72 (0.33)	194 (0.32)	
40-49 y	935 (4.34)	2965 (4.88)	
50-59 y	3517 (16.31)	9591 (15.78)	
60-69 y	9418 (43.68)	28,738 (47.29)	
70-75 y	7617 (35.33)	19,285 (31.73)	
Sex (%)			<.001
Men	10,083 (46.77)	30,990 (50.99)	
Women	11,476 (53.23)	29,783 (49.01)	
Alcohol drinking (No. [%])			<.001
None/mild	16,536 (76.7)	44,926 (73.92)	
Moderate	4319 (20.03)	13,646 (22.45)	
Heavy	704 (3.27)	2201 (3.62)	
Smoking (No. [%])			<.001
Nonsmoker	14,309 (66.37)	38,851 (63.93)	
Former smoker	3961 (18.37)	12,268 (20.19)	
Current smoker	3289 (15.26)	9654 (15.89)	
Glucose (mg/dL [mmol/L]), mean ± SD	139.71±49.17 (7.75±2.73)	141.62±48.55 (7.86±2.69)	<.001
Systolic blood pressure (mm Hg), mean ± SD	128.69±16.14	128.76±15.8	.57
Diastolic blood pressure (mm Hg), mean ± SD	76.54±10.03	76.86±9.9	<.001
Estimated glomerular filtration rate, mean ± SD[b]	48±8.77	52.6±8.07	<.001
Total cholesterol (mg/dL [mmol/L]), mean ± SD	179.24±43.16 (4.64±1.12)	178.5±41.91 (4.62±1.09)	.03
Other antidiabetic treatment (No. [%])			
Insulin	4062 (18.84)	9934 (16.35)	<.001
Sulfonylurea	12,867 (59.68)	38,512 (63.37)	<.001
Metformin	12,672 (58.78)	39,111 (64.36)	<.001
Meglitinide	451 (2.09)	1111 (1.83)	.02
Thiazolidinediones	2069 (9.6)	5597 (9.21)	.09
Acarbose	1680 (7.79)	4844 (7.97)	.41

[a]Derived from the *t* test for continuous variables or the χ^2 test for categorical variables.
[b]Estimated glomerular filtration rates are estimated using the Modification of Diet in Renal Disease equation.

for available confounding factors, adjusted HRs for death in patients who were prescribed the inappropriate dose of DPP-4 inhibitor were virtually unaffected in CKD stage 3 (1.12; 95% CI, 1.005-1.248; *P*=.04), but adjusted HRs for death in the group that received the inappropriate dose of DPP-4 inhibitors was not significant in CKD stage 4 (0.885; 95% CI, 0.617-1.27; *P*=.51). The adjusted HRs for ED visits and severe hypoglycemia in the inappropriate dosing group increased with increasing CKD stage. In multivariable Cox proportional hazards regression modeling, adjusted HRs for ED visits and severe hypoglycemia were 1.056 (95% CI, 0.999-1.116; *P*=.05) and 1.131 (95% CI, 0.993-1.289; *P*=.06), respectively, in patients with CKD stage 3 with inappropriate DPP-4 inhibitor dosing and 1.252 (95% CI, 0.987-1.588; *P*=.06)

TABLE 2. Risk of Death, Emergency Department Visits, and Severe Hypoglycemia in Patients With Type 2 Diabetes and Chronic Kidney Disease (Stage 3 or 4) by Cox Proportional Hazards Regression Analysis[a]

Variable	Patients (No.)	Events (No.)	Duration (person-days)	Rate (No. [95% CI] of events per 1000 person-days)	Model 1		Model 2		Model 3	
					Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Severe hypoglycemia										
Appropriate dosing group	60,773	805	78,644.02	10.24 (9.55-10.97)	1 (Reference)		1 (Reference)		1 (Reference)	
Inappropriate dosing group	21,559	372	29,662.12	12.54 (11.33-13.88)	1.199 (1.061-1.357)	.004	1.194 (1.056-1.351)	.004	1.192 (1.054-1.349)	.005
Emergency department visits										
Appropriate dosing group	60,773	4845	75,095.49	64.52 (62.73-66.36)	1 (Reference)		1 (Reference)		1 (Reference)	
Inappropriate dosing group	21,559	1885	28,310.03	66.58 (63.65-69.66)	1.076 (1.02-1.135)	.007	1.072 (1.017-1.131)	.01	1.074 (1.018-1.133)	.009
Death										
Appropriate dosing group	60,773	1134	80,202.27	14.14 (13.34-14.99)	1 (Reference)		1 (Reference)		1 (Reference)	
Inappropriate dosing group	21,559	529	30,514.98	17.34 (15.92-18.88)	1.149 (1.036-1.275)	.008	1.142 (1.03-1.267)	.01	1.115 (1.005-1.237)	.04

[a]Model 1 is adjusted for age, sex, and history of emergency department visits or severe hypoglycemia events. Model 2 is adjusted for age, sex, smoking and alcohol drinking status, systolic blood pressure, total cholesterol level, and history of emergency department visits or severe hypoglycemia events. Model 3 is adjusted for age, sex, smoking and alcohol drinking status, systolic blood pressure, total cholesterol level, other antidiabetic drug treatment, and history of emergency department visits or severe hypoglycemia events.

and 1.609 (95% CI, 1.065-2.432; *P*=.02) in patients with CKD stage 4 with inappropriate DPP-4 inhibitor dosing (Figure 2).

Subgroup Analyses by Other Antidiabetic Medication Prescriptions

Furthermore, subgroup analyses were performed by other antidiabetic medication prescription patterns. First, we analyzed the safety of an inappropriate dose of DPP-4 inhibitor monotherapy. Analysis of patients with T2DM and CKD on only DPP-4 inhibitor monotherapy revealed that the risks of death (HR=0.928; 95% CI, 0.648-1.33; *P*=.69), ED visits (HR=1.011; 95% CI, 0.878-1.164; *P*=.88), and severe hypoglycemia (HR=1.243; 95% CI, 0.683-2.263; *P*=.48) were not different between the appropriate and inappropriate dosing groups. In dual therapy with DPP-4 inhibitor and metformin, the adjusted HR of deaths (HR=1.448; 95% CI, 1.112-1.886; *P*=.006) and ED visits (HR=1.146; 95% CI, 1.007-1.305; *P*=.04) were significantly higher in the inappropriate dosing group than in the appropriate dosing group. However, the adjusted HR of severe hypoglycemia in the inappropriate dosing group was not significantly different compared with the appropriate dosing group (HR=1.485; 95% CI, 0.918-2.403; *P*=.11). In patients treated with a combination of DPP-4 inhibitor, metformin, and other antidiabetic medications, the risks of death (HR=1.149; 95% CI, 1.02-1.294; *P*=.02), ED visits (HR=1.094; 95% CI, 1.026-1.167; *P*=.006), and severe hypoglycemia (HR=1.237; 95% CI, 1.086-1.41; *P*=.001) were significantly higher in the inappropriate dosing group than in the appropriate dosing group after adjusting for all available confounding factors (Figure 2).

DISCUSSION

The findings from this nationwide cohort study were that inappropriate dosing with DPP-4 inhibitors was associated with a 15% increased risk of death from all causes in patients with T2DM with CKD stage 3 or 4 compared with appropriate dosing with DPP-4 inhibitors. These findings were supported by the observations that inappropriate dosing with DPP-4 inhibitors was

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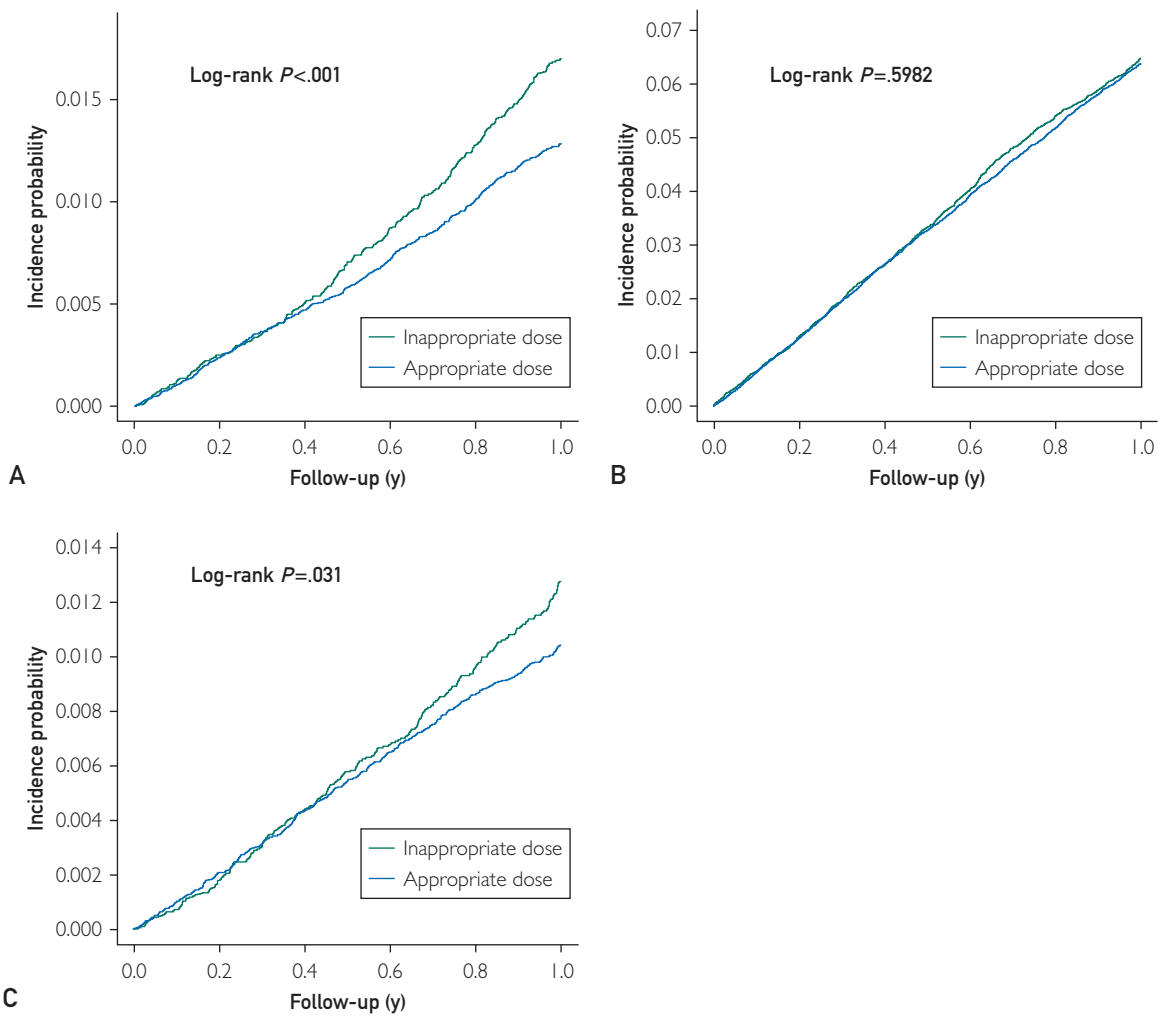

FIGURE 1. Kaplan-Meier survival curves for all-cause mortality (A), emergency department visits (B), and severe hypoglycemia (C) in patients with type 2 diabetes mellitus and chronic kidney disease according to appropriate and inappropriate dosing of dipeptidyl peptidase-4 inhibitors.

accompanied by a 7.6% increased risk of ED visits and a 19.9% increased risk of severe hypoglycemia, whereas risks of ED visits and severe hypoglycemia in patients treated with inappropriate doses of DPP-4 inhibitor increased with an increase in CKD stage in subgroup analysis. Risk of death, ED visits, and severe hypoglycemia with appropriate DPP-4 inhibitor dosage persisted after adjustment for possible confounders. Although the results of an observational study should be interpreted with caution, the questions that the present study asks cannot be answered with a prospective controlled design. Furthermore, to our knowledge, this nationwide observational study of 82,332 patients with T2DM and CKD is the first and largest to examine the associations between death from all causes, number of ED visits, and number of episodes of severe hypoglycemia according to appropriate or inappropriate dosing with DPP-4 inhibitors.

The DPP-4 inhibitors have advantages over older agents, which can cause weight gain and tend to cause hypoglycemia, and are, therefore, a welcome addition as second-line therapy in patients when

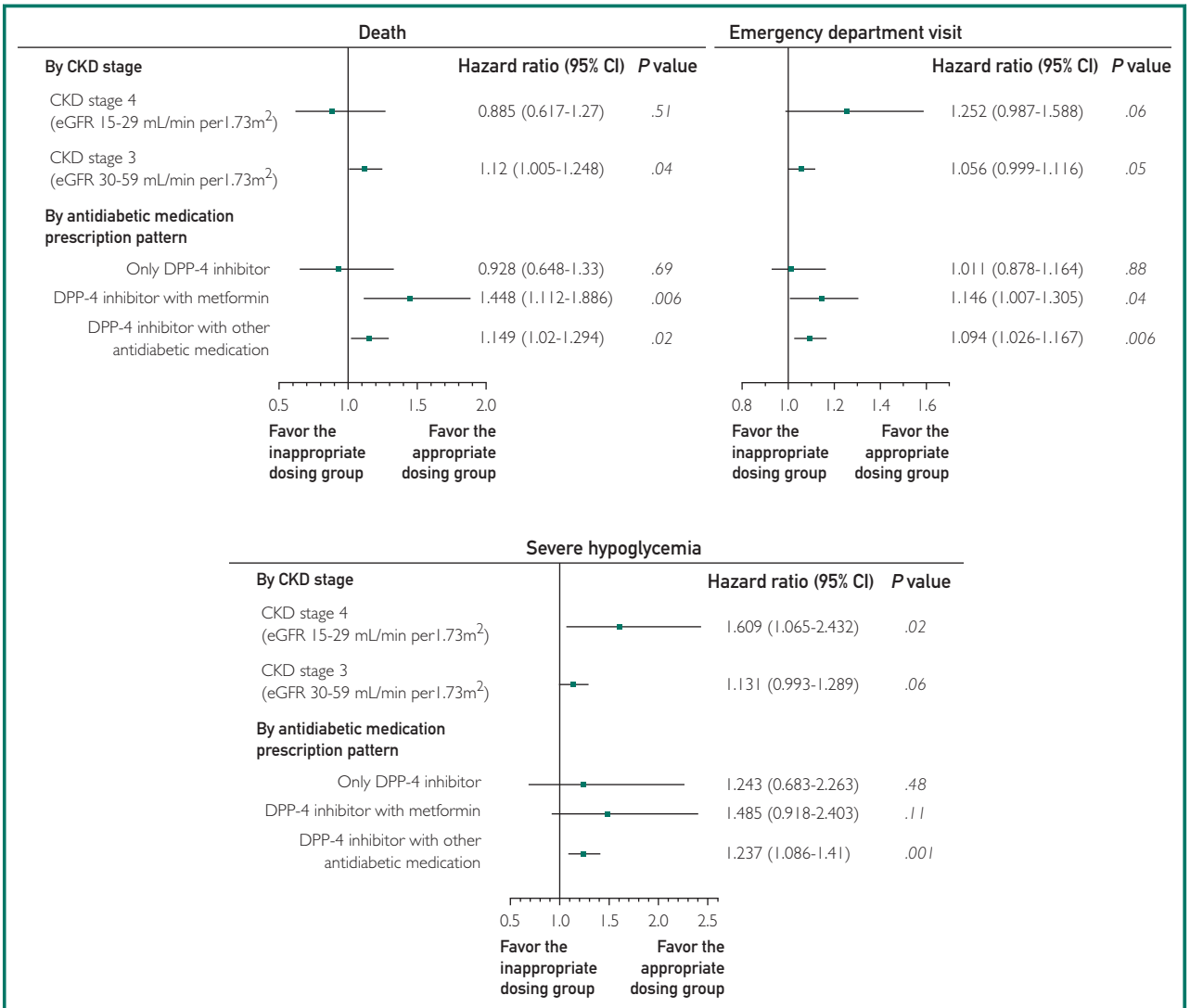

FIGURE 2. Risk of death, emergency department visits, and severe hypoglycemia in patients with type 2 diabetes mellitus and chronic kidney disease (CKD) (stage 3 or 4) by patterns of medication prescription using Cox proportional hazards regression analysis while controlling for baseline covariates. All the analyses were adjusted for age, sex, smoking and alcohol drinking status, systolic blood pressure, total cholesterol level, other antidiabetic drug treatment, and history of emergency department visits or severe hypoglycemia events. DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate (estimated using the Modification of Diet in Renal Disease equation).

metformin is no longer sufficient.[14,15] A meta-analysis clearly found the glycated hemoglobin–lowering ability of DPP-4 inhibitors (−0.52%; 95% CI, −0.64 to −0.39) in patients with T2DM and CKD stages 3 and 4 and the low prevalence of adverse events.[16,17] Long-term studies as well as data from the largest trials available, namely, TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin),[18] EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care),[19] and SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53),[20] have confirmed the efficacy and safety of these agents in patients with CKD; therefore, DPP-4 inhibitors are currently widely prescribed in patients with CKD.[15] Pharmacokinetic studies of other

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DPP-4 inhibitors have recommended dose reduction according to renal function to avoid drug accumulation, with a few exceptions (eg, linagliptin). The unintended use of conventional doses in patients with CKD will lead to an increase in plasma concentrations according the type and extent of renal impairment. According to toxicological studies in animals, the no observed adverse effect levels based on area under the curve and maximum concentration for outcomes in animals treated with sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin were 6 or more, 7 or more, more than 29, more than 27, and 40 or more times higher than the usual clinical levels, respectively. Hence, DPP-4 inhibitors are considered to have a wide therapeutic margin.[21] In human studies, similar findings have been reported for initial phase 2 dose-finding studies, although very high doses have typically been single dose or short-term, and studies have enrolled either healthy volunteers or people with T2DM with normal renal function. All previously published phase 2 dose-finding studies with various kinds of DPP-4 inhibitors reported that this class of drugs is safe and well tolerated. Furthermore, these findings suggest that inadvertent overtreatment of patients with CKD with DPP-4 inhibitors is unlikely to result in deleterious outcomes.[21] Although we found that inadvertent overtreatment of patients with CKD with DPP-4 inhibitors resulted in adverse outcomes such as increased mortality, ED visits, and severe hypoglycemia, monotherapy with an inappropriate dose of DPP-4 inhibitor was not associated with deleterious outcomes, consistent with the phase 2 dose-finding studies (Figure 2). However, a combination of DPP-4 inhibitors and other antidiabetic drugs, even metformin, elicited adverse outcomes, suggesting that there may be some crosstalk between DPP-4 inhibitors and other diabetic drugs. The efficacy and safety of DPP-4 inhibitor and metformin combination therapy had been proved by many multicenter, randomized, double-blind, placebo-controlled trials.[22] Adding DPP-4 inhibitors to metformin therapy was not inferior to adding glimepiride or glipizide in lowering glycated hemoglobin levels in patients with T2DM.[23-25] In addition, adding DPP-4 inhibitors to metformin produced outcomes similar to metformin monotherapy and superior outcomes to those obtained when glimepiride or glipizide were added in terms of safety and incidence of hypoglycemia.[23-27] Similar to previous studies that showed that combination therapy with metformin and DPP-4 inhibitor was safe and efficacious, the present subgroup analysis showed that the risks of death, ED visits, and severe hypoglycemia in patients dosed appropriately with DPP-4 inhibitor and metformin were not different from those obtained with appropriate dosing of DPP-4 inhibitor as monotherapy (P=.25, P=.36, P=.48, respectively). Moreover, patients treated with an appropriate dose of DPP-4 inhibitor and metformin had 30% lower mortality (95% CI, 0.521-0.962; P=.027) than those treated with an inappropriate dose of DPP-4 inhibitors and metformin. Therefore, when prescribing combinations of antidiabetic drugs, DPP-4 inhibitors should be prescribed according to renal function and manufacturer guidelines.

Hypoglycemia is the most common and important treatment-related adverse event in patients with diabetes. Many previous studies have established that patients with T2DM and CKD have an increased risk of hypoglycemia, which is also associated with an excessive mortality rate in these patients. According to a large retrospective observational study of 243,222 patients followed up at the Veterans Health Administration who had 2,040,206 glucose measurements, with mortality determined 1 day after glucose measurement, the risk of hypoglycemia in a patient with T2DM and CKD was 2-fold greater than that of a patient with T2DM without CKD, and the risk of 1-day mortality also increased with hypoglycemia.[8] During the past decade, 3 large prospective trials—ACCORD[28] (Action to Control Cardiovascular Risk in Diabetes), ADVANCE[29] (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), and VADT[30] (Veterans Affairs Diabetes Trial)—have found that an event of severe hypoglycemia is associated with increased risk of

subsequent mortality. In ACCORD, those who experienced severe hypoglycemia episodes had higher rates of death than those without such episodes (HR=1.41; 95% CI, 1.03-1.93).[31] In VADT, a recent severe hypoglycemia episode was the strongest independent predictor of death at 90 days.[30] Although we did not analyze the direct association between hypoglycemia and mortality, the incidence of severe hypoglycemia and mortality increased in parallel in patients with T2DM and CKD who were prescribed an inappropriate dose of DPP-4 inhibitor, had a lower eGFR, or received a multidrug combination.

In subgroup analysis of patients with T2DM and CKD stage 4, there was no difference in mortality between patients who received appropriate vs inappropriate doses of DPP-4 inhibitor, inconsistent with the present primary study findings. Possible reasons for this may be that there were only 2671 persons (3.2% of the study population) with T2DM and CKD stage 4. This sample size may have been too small to accurately determine the relationship between mortality and DPP-4 inhibitor dosing in patients with CKD stage 4. Second, patients with T2DM and CKD stage 4 had 2- to 3-fold higher mortality rates than patients with T2DM and CKD stage 3 in the present study. Increased mortality due to other causes may also have confounded the association between death and DPP-4 inhibitor dosing in these patients. Third, an appropriate DPP-4 inhibitor dose for patients with CKD stage 3 might be inappropriate and harmful in patients with CKD stage 4. A previous study of a single dose of sitagliptin showed that the area under the plasma concentration curve from time 0 extrapolated to infinity was approximately 3.8-fold higher for CKD stage 4 relative to the normal renal function controls.[32] Hence, the dose of sitagliptin was decreased to be one-quarter of that prescribed to patients with T2DM and normal renal function. However, that same study also showed that time after administration of a drug when the maximum plasma concentration is reached and terminal half-life increased with decreasing renal function and that in clinical practice, a multiple-dose situation is more likely than a single-dose situation; thus, this dose reduction could be insufficient.

Rates of nonadherence to renal dosing guidelines vary according to methodological approach. A systemic review by Long et al[33] in 2004 of 6 studies that addressed adherence to renal dose adjustment found that the rate of nonadherence to renal dosing guidelines in ambulatory care was 70%. A recent systemic review of 18 studies that addressed adherence to renal dose adjustment showed that the prevalence of renally inappropriate drug use ranged from 1% to 37% in outpatient settings.[34] Similar to this previous study, we found that the prevalence of inappropriate dosing with DPP-4 inhibitors varied from 24% to 43%. Although the prevalence of inappropriate dosing with DPP-4 inhibitors decreased over time due to increasing use of DPP-4 inhibitors that do not require dosage adjustment with CKD stage, the prevalence of inappropriate dosing with DPP-4 inhibitors requiring dosage adjustment for all stages of CKD did not change during the study. A recent systemic review of 49 studies reported that only 1 study found an association between inappropriate drug use and mortality in patients with CKD. Breton et al[35] reported that exposure to an inappropriate dose of drugs was independently associated with higher all-cause mortality (HR=1.4; 95% CI, 1.0-1.9). In the present study, we analyzed only the inappropriate dosing of DPP-4 inhibitors and found that this was independently associated with higher all-cause mortality (HR=1.15; 95% CI, 1.04-1.28).

To our knowledge, this is the first observational study to examine the associations between death from all causes, ED visits, and incidence of severe hypoglycemia episodes with appropriate or inappropriate dosing with DPP-4 inhibitors. The strengths of this study are its large size and national representation. In addition, the present results were consistent across sensitivity and subgroup analyses. This study also has some limitations. First, it was a retrospective observational study and, as such, was prone to the limitations inherent to this study design. Real-world

patients may differ in many aspects from the patients in a controlled study. Although the analyses were adjusted for most available demographic and clinical variables, data on potentially significant confounders, such as overall glucose level, information about the appropriateness of other classes of medications, and other medical care, were not available for adjustment. Second, medication adherence was not considered because the database contains only information about filled prescriptions. Third, due to the retrospective design, CKD stages determined by the single-time measurement of serum creatinine level can misclassify patients and be changed during the observed period. Fourth, with respect to the risk of hypoglycemia, inappropriate dosing of other antidiabetic drugs, especially sulfonylurea, could be a bias in this study even after we adjusted for antidiabetic drug treatment in multivariable Cox proportional hazards regression modeling. Finally, this study did not address the mechanisms linking inappropriate doses of DPP-4 inhibitor and associated death, ED visits, or severe hypoglycemia. Although randomized controlled studies are needed to confirm or disprove these results, clinical trials to test the safety of inappropriate dosing in patients with T2DM and CKD with DPP-4 inhibitors may not be possible. The high-quality observational data provided by the present study, therefore, may represent the most readily available, highest level of evidence for this situation.

CONCLUSION

The analysis of nationwide data from patients with T2DM and CKD stage 3 revealed that inappropriate dosing with DPP-4 inhibitor was associated with a statistically significantly higher risk of death from all causes compared with treatment with an appropriate dose of DPP-4 inhibitor; however, this held true only for combination therapy (dual and higher), not monotherapy with DPP-4 inhibitor. Inappropriate DPP-4 inhibitor dosing was also associated with a significantly higher risk of ED visits and severe hypoglycemia in patients with T2DM and CKD stages 3 and 4 than treatment with an appropriate dose of DPP-4 inhibitor. The present results have important therapeutic implications for the prescription of DPP-4 inhibitors in patients with T2DM and CKD stage 3 or 4.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ACCORD** = Action to Control Cardiovascular Risk in Diabetes; **ADVANCE** = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; **CKD** = chronic kidney disease; **DPP-4** = dipeptidyl peptidase-4; **eGFR** = estimated glomerular filtration rate; **EXAMINE** = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; **HR** = hazard ratio; **MDRD** = Modification of Diet in Renal Disease; **NHID** = National Health Information Database; **SAVOR-TIMI 53** = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53; **SD** = standard deviations; **T2DM** = type 2 diabetes mellitus; **TECOS** = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; **VADT** = Veterans Affairs Diabetes Trial

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